NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 452

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL
(FR-1138®)

(CAS NO. 3296-90-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Listings of all published NTP reports and ongoing studies are also available from NTP Central Data Management. The Abstracts and other study information for 2-year studies are also available on the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

NTP TECHNICAL REPORT

ON THE

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May 1996

NTP TR 452

NIH Publication No. 96-3368

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

J.K. Dunnick, Ph.D., Study Scientist
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
M.R. Elwell, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
J.K. Haseman, Ph.D.
J.R. Hailey, D.V.M.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

American Biogenics Corporation

Conducted studies, evaluated pathology findings for 13-week studies in rats and mice

I.A. Muni, Ph.D., Principal Investigator
R. Dahlgren, Ph.D., D.V.M., Pathologist

Southern Research Institute

Conducted studies, evaluated pathology findings for 2-year studies in rats and mice

J.D. Prejean, Ph.D., Principal Investigator
D.R. Farnell, D.V.M., Ph.D., Pathologist (rats)
J.E. Heath, D.V.M., Pathologist (mice)

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
H.R. Brown, D.V.M., M.S.
K. Yoshitomi, D.V.M., Ph.D.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides, prepared pathology report for 13-week studies in rats and mice (13 August 1987)

P.K. Hildebrandt, D.V.M., Chair
PATHCO, Inc.
H.R. Brown, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
J. Everitt, D.V.M.
Chemical Industry Institute of Toxicology
M.P. Jokinen, D.V.M.
National Toxicology Program
J. Mahler, D.V.M.
National Toxicology Program

Evaluated slides, prepared pathology report for 2-year studies in rats (15 July 1993)

J.C. Seely, D.V.M., Chair
PATHCO, Inc.
A. Enomoto, D.V.M., Observer
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.
Chemical Industry Institute of Toxicology
S. Mery, D.V.M., Observer
Chemical Industry Institute of Toxicology
R. Sills, D.V.M., Ph.D.
National Toxicology Program
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

Evaluated slides, prepared pathology report for 2-year studies in mice (25 February 1993)

M.A. Stedham, D.V.M., Chair
Pathology Associates, Inc.
G.A. Boorman, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J. Mahler, D.V.M.
National Toxicology Program
D. Wolf, D.V.M., Ph.D.
Chemical Industry Institute of Toxicology
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

Analytical Sciences, Inc.

Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
N.G. Mintz, B.S.
S. Rosenblum, M.S.

Biotechnical Services, Inc.

Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
J.R. Carlton, B.A.
S.R. Gunnels, M.A.
E.S. Rathman, M.S.

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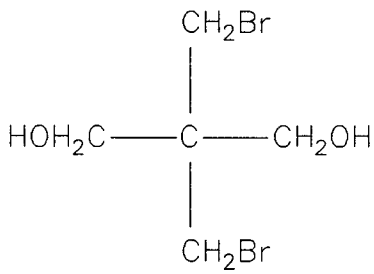
ABSTRACT



2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL
(FR-1138®)

(Technical Grade: 78.6% 2,2-bis(bromomethyl)-1,3-propanediol, 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane, 6.9% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane, 0.2% pentaerythritol, and 7.7% dimers and structural isomers)

CAS No. 3296-90-0

Chemical Formula: $C_5H_{10}Br_2O_2$ Molecular Weight: 261.94

Synonyms: 2,2-Bis(2-bromomethyl)-1,3-propanediol; 1,3-dibromo-2,2-dihydroxymethylpropane; 1,3-dibromo-2,2-dimethylolpropane; 2,2-dibromomethyl-1,3-propanediol; dibromopentaerythritol; dibromoneopentyl glycol; pentaerythritol dibromide; pentaerythritol dibromohydrin

2,2-Bis(bromomethyl)-1,3-propanediol is used as a fire retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam. 2,2-Bis(bromomethyl)-1,3-propanediol was chosen for study because it is a widely used flame retardant and little toxicity and carcinogenicity data were available.

Groups of male and female F344/N rats and B6C3F$_1$ mice were exposed to technical grade 2,2-bis(bromomethyl)-1,3-propanediol (78.6% pure) in feed for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow, and mouse peripheral blood.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were fed diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks. These levels corresponded to approximately 100, 200, 400, 800, or 1,700 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight (males) and 100, 200, 400, 800, or 1,600 mg/kg (females). No rats died during the studies. The final mean body weights and weight gains of 5,000, 10,000, and 20,000 ppm males and females were significantly lower than those of the controls. Feed consumption by exposed animals was lower than that by controls at week 1, but was generally similar to or slightly higher than that by controls at week 13. No chemical-related clinical findings were observed. Chemical-related differences in clinical pathology parameters included increased urine volumes accompanied by decreased urine specific gravity and minimally increased protein excretion in 10,000 and 20,000 ppm males. In females, urine parameters were less affected than males. Water deprivation tests demonstrated that male and female rats were able to adequately concentrate their urine in response

to decreased water intake. Serum protein and albumin concentrations in female rats exposed to 2,500 ppm and higher were slightly lower than those of the controls. Renal papillary degeneration was present in 5,000 and 10,000 ppm males, and in 20,000 ppm males and females. Hyperplasia of the urinary bladder was present in 20,000 ppm males.

13-Week Study in Mice

Groups of 10 male and 10 female mice were fed diets containing 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks. These levels corresponded to approximately 100, 200, 500, 1,300, or 3,000 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight (males) and 140, 300, 600, 1,200, or 2,900 mg/kg (females). One control female, two males and one female receiving 625 ppm, one female receiving 1,250 ppm, one female receiving 2,500 ppm, one female receiving 5,000 ppm, and three males receiving 10,000 ppm died during the study. The final mean body weights and body weight gains of males and females receiving 1,250, 2,500, 5,000, or 10,000 ppm and of females receiving 625 ppm were significantly lower than those of the controls. Feed consumption by exposed mice was generally higher than that by controls throughout the study. Clinical findings included abnormal posture and hypoactivity in 10,000 ppm male and female mice. Blood urea nitrogen concentrations of 5,000 ppm females and 10,000 ppm males and females were greater than those of controls. Also, urine specific gravity was lower in 10,000 ppm females. Differences in organ weights generally followed those in body weights. Papillary necrosis, renal tubule regeneration, and fibrosis were observed in the kidneys of 2,500 and 5,000 ppm males and 10,000 ppm males and females. Urinary bladder hyperplasia was observed in 5,000 and 10,000 ppm males and females.

2-Year Study in Rats

Groups of 60 male and 60 female rats received 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Groups of 70 males and 60 females received 0 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. A stop-exposure group of 70 male rats received 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 3 months, after which animals received undosed feed for the remainder of the 2-year study. Average daily doses of 2,2-bis(bromomethyl)-1,3-propanediol were 100, 200, or 430 mg/kg body weight for males and 115, 230, or 460 mg/kg for females. Stop-exposure males received an average daily dose of 800 mg/kg. Ten animals from the 0 ppm male group and the 20,000 ppm stop-exposure group were evaluated at 3 months; nine or 10 control animals and five to nine animals from each of the continuous-exposure groups were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 5,000 and 10,000 ppm continuous-exposure study males and females and 20,000 ppm stop-exposure males was significantly lower than that of the controls. Mean body weights of exposed male and female rats receiving 10,000 ppm and stop-exposure males receiving 20,000 ppm were lower than those of the controls throughout most of the study. In the continuous-exposure study, feed consumption by exposed rats was generally similar to that by controls throughout the study. In 20,000 ppm stop-exposure males, the feed consumption was lower than that by controls. Clinical findings included skin and/or subcutaneous masses on the face, tail, and the ventral and dorsal surfaces of exposed rats.

Pathology Findings

In the 2-year continuous and stop-exposure studies in male rats, exposure to 2,2-bis(bromomethyl)-1,3-propanediol was associated with neoplastic effects in the skin, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland, hematopoietic system, and seminal vesicle. Nonneoplastic effects in the kidney, lung, thyroid gland, seminal vesicle, pancreas, urinary bladder, and forestomach were also observed. In females, 2-year exposure to 2,2-bis(bromomethyl)-1,3-propanediol was associated with neoplastic effects in the oral cavity, esophagus, mammary gland, and thyroid gland. Nonneoplastic effects in the kidney were also observed. These findings are outlined in the two summary tables.

2-YEAR STUDY IN MICE

Groups of 60 male and 60 female mice received 0, 312, 625, or 1,250 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Average daily doses of 2,2-bis(bromomethyl)-1,3-propanediol were 35, 70, or 140 mg/kg (males) and 40, 80, or 170 mg/kg (females). Eight to 10 animals from each group were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 1,250 ppm males and females was significantly lower than that of the controls. Mean body weights of exposed male and female mice were similar to controls throughout the study. Final mean body weights were also generally similar to those of controls. Feed consumption by exposed male and female mice was similar to that by controls. Clinical findings included tissue masses involving the eye in exposed mice.

Pathology Findings

Exposure of male mice to 2,2-bis(bromomethyl)-1,3-propanediol for 2 years was associated with neoplastic effects in the harderian gland, lung, and kidney. Exposure of female mice to 2,2-bis(bromomethyl)-1,3-propanediol was associated with increased incidences of neoplasms of the harderian gland, lung, and skin. Nonneoplastic effects in the lung were also observed in exposed females. These findings are outlined in the two summary tables.

GENETIC TOXICOLOGY

2,2-Bis(bromomethyl)-1,3-propanediol was mutagenic in *Salmonella typhimurium* strain TA100 when tested in the presence of induced 30% hamster liver S9; all other strain/activation combinations gave negative results. In cultured Chinese hamster ovary cells, 2,2-bis(bromomethyl)-1,3-propanediol induced chromosomal aberrations only in the presence of S9; no induction of sister chromatid exchanges was observed in cultured Chinese hamster ovary cells after treatment with 2,2-bis(bromomethyl)-1,3-propanediol, with or without S9. *In vivo*, 2,2-bis(bromomethyl)-1,3-propanediol induced significant increases in the frequencies of micronucleated erythrocytes in male and female mice. Significant increases in micronuclei were observed in peripheral blood samples from male and female mice exposed to 2,2-bis(bromomethyl)-1,3-propanediol for 13 weeks via dosed feed. Results of a bone marrow micronucleus test in male mice, where 2,2-bis(bromomethyl)-1,3-propanediol was administered by gavage, were considered to be equivocal due to inconsistent results obtained in two trials. An additional bone marrow micronucleus test was performed with male and female mice and 2,2-bis(bromomethyl)-1,3-propanediol was administered as a single intraperitoneal injection; results of this test were positive in females and negative in males.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of 2,2-bis-(bromomethyl)-1,3-propanediol (FR-1138®) in male F344/N rats based on increased incidences of neoplasms of the skin, subcutaneous tissue, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland, and seminal vesicle, and the increased incidence of mononuclear cell leukemia.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female F344/N rats based on increased incidences of neoplasms of the oral cavity, esophagus, mammary gland, and thyroid gland.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in male B6C3F$_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and kidney.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female B6C3F$_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and subcutaneous tissue.

Slight increases in the incidences of neoplasms of the pancreas and kidney in male rats; forestomach in male mice; and forestomach, mammary gland, and circulatory system in female mice may have also been related to treatment.

Exposure of male and female rats to 2,2-bis(bromomethyl)-1,3-propanediol was associated with alveolar/bronchiolar hyperplasia in the lung (males only); focal atrophy, papillary degeneration, transitional epithelial hyperplasia (pelvis), and papillary epithelial hyperplasia in the kidney; follicular cell hyperplasia in the thyroid gland (males only); hyperplasia in the seminal vesicle and pancreas (males only); mucosal hyperplasia in the forestomach (males only); and urinary bladder hyperplasia (males only). Exposure of mice to 2,2-bis(bromomethyl)-1,3-propanediol was associated with hyperplasia of the alveolar epithelium in females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

Summary of Site-Specific Carcinogenic Effects in Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

	Male Rats	Female Rats	Male Mice	Female Mice
Site				
Skin	+	−	−	−
Subcutaneous tissue	+	−	−	+
Mammary gland	+	+	−	±
Zymbal's gland	+	−	−	−
Oral cavity	+	+	−	−
Esophagus	+	+	−	−
Forestomach	+	−	±	±
Small intestine	+	−	−	−
Large intestine	+	−	−	−
Mesothelium	+	−	−	−
Kidney	±	−	+	−
Urinary bladder	+	−	−	−
Lung	+	−	+	+
Thyroid gland	+	+	−	−
Seminal vesicle	+	NA	−	NA
Hematopoietic system	+	−	−	−
Pancreas	±	−	−	−
Harderian gland	−	−	+	+
Circulatory system	−	−	−	±

+ = some or clear evidence
± = equivocal evidence
− = no evidence
NA = not applicable

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 2,500, 5,000, or 10,000 ppm and 20,000 ppm stop-exposure (equivalent to 0, 100, 200, or 430 mg/kg and 800 mg/kg)	0, 2,500, 5,000, or 10,000 ppm (equivalent to 0, 115, 230, or 460 mg/kg)	0, 312, 625, or 1,250 ppm (equivalent to 0, 35, 70, or 140 mg/kg)	0, 312, 625, or 1,250 ppm (equivalent to 0, 40, 80, or 170 mg/kg)
Body weights	10,000 ppm and 20,000 ppm stop-exposure groups lower than controls	10,000 ppm group lower than controls	Exposed groups similar to controls	Exposed groups similar to controls
2-Year survival rates	26/51, 20/53, 13/51, 1/55, 0/60	36/50, 27/51, 23/53, 5/52	42/50, 36/51, 35/50, 30/48	37/52, 30/50, 26/51, 11/50
Nonneoplastic effects	Kidney: focal atrophy (0/51, 0/53, 0/51, 5/55, 0/59); papillary degeneration (0/51, 5/53, 30/51, 29/55, 16/59); papillary epithelial hyperplasia (10/51, 20/53, 25/51, 47/55, 21/59); pelvis, transitional epithelium, hyperplasia (0/51, 0/53, 0/51, 4/55, 4/59) Lung: alveolar/ bronchiolar hyperplasia (3/51, 4/53, 5/51, 7/55, 14/60) Thyroid gland: follicular cell hyperplasia (1/51, 0/53, 2/51, 5/55, 6/59) Seminal vesicle: hyperplasia (1/51, 6/53, 4/51, 16/55, 33/60) Pancreas: focal hyperplasia (3/51, 9/53, 12/51, 14/53, 27/59) Forestomach: mucosal hyperplasia (4/51, 12/53, 6/51, 6/55, 6/59) Urinary bladder: hyperplasia (0/51, 0,53, 1/51, 3/55, 10/59)	Kidney: focal atrophy (0/50, 2/51, 1/53, 7/52); papillary degeneration (0/50, 1/51, 3/53, 17/52); papillary epithelial hyperplasia (0/50, 1/51, 1/53, 7/52)	None	Lung: alveolar epithelium, hyperplasia (1/52, 3/50, 8/51, 15/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Skin: squamous cell papilloma, keratoacanthoma, trichoepithelioma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (4/51, 6/53, 14/51, 24/55, 21/60) Skin, subcutaneous tissue: fibroma, fibrosarcoma, or sarcoma (2/51, 9/53, 13/51, 16/55, 10/60) Mammary gland: fibroadenoma or adenoma (0/51, 4/53, 7/51, 7/55, 5/60) Zymbal's gland: adenoma or carcinoma (2/51, 1/53, 4/51, 5/55, 15/60) Oral cavity (pharynx, tongue, or gingiva): squamous cell papilloma or carcinoma (0/51, 4/53, 9/51, 10/55, 13/60) Esophagus: squamous cell papilloma (0/51, 0/53, 1/51, 5/55, 0/60) Forestomach: squamous cell papilloma (0/51, 0/53, 0/51, 1/55, 5/60) Large intestine: adenoma or carcinoma (0/51, 0/53, 3/51, 4/55, 11/59) Small intestine: adenoma or carcinoma (0/51, 0/53, 0/51, 2/53, 5/59) Malignant mesothelioma: (0/51, 3/53, 8/51, 9/55, 26/60) Urinary bladder: transitional cell papilloma or carcinoma (0/51, 0/53, 1/51, 3/55, 2/59)	Oral cavity: squamous cell papilloma or carcinoma (2/50, 3/51, 5/53, 6/52) Esophagus: squamous cell papilloma (0/50, 0/51, 1/53, 10/52) Mammary gland: fibroadenoma (25/50, 45/51, 46/53, 45/52) Thyroid gland: follicular cell adenoma or carcinoma (0/50, 0/51, 2/53, 4/52)	Harderian gland: adenoma or carcinoma (4/50, 7/51, 16/50, 22/49) Lung: alveolar/ bronchiolar adenoma or carcinoma (15/50, 11/51, 16/50, 25/49) Kidney (renal tubule): adenoma (0/50, 0/51, 3/50, 2/49)	Harderian gland: adenoma or carcinoma (3/52, 12/50, 13/51, 19/50) Lung: alveolar/ bronchiolar adenoma or carcinoma (5/52, 5/50, 15/51, 19/50) Skin (subcutaneous tissue): sarcoma (0/52, 1/50, 4/51, 11/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects (continued)	Lung: alveolar/ bronchiolar adenoma or carcinoma (1/51, 1/53, 3/51, 4/55, 7/60); squamous cell carcinoma (0/51, 0/53, 0/51, 0/55, 3/60) Thyroid gland: follicular cell adenoma or carcinoma (0/51, 2/53, 6/51, 3/55, 9/59) Seminal vesicle: adenoma or carcinoma (0/51, 0/53, 0/51, 0/55, 2/60) Hematopoietic system: mononuclear cell leukemia (27/51, 29/53, 40/51, 34/55, 25/60)			
Uncertain effects	Kidney (renal tubule): adenoma (0/51, 0/53, 1/51, 3/55, 1/59) Pancreas: acinar cell adenoma (1/51, 2/53, 4/51, 3/53, 3/59)	None	Forestomach: squamous cell papilloma or carcinoma (0/50, 3/51, 3/50, 4/49)	Mammary gland: carcinoma (0/52, 0/50, 1/51, 3/50) Forestomach: squamous cell papilloma (0/52, 1/50, 5/51, 3/50) Circulatory system: hemangioma and hemangiosarcoma (1/52, 2/50, 0/51, 5/50)
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Positive with S9 in strain TA100; negative in strains TA98, TA1535, and TA1537 with and without S9
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9
Micronucleated erythrocytes Mouse bone marrow *in vivo* by gavage:	Equivocal in male mice
Mouse bone marrow *in vivo* by intraperitoneal injection:	Negative in male and positive in female mice
Mouse peripheral blood *in vivo*:	Positive in male and female mice

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 2,2-bis(bromomethyl)-1,3-propanediol on November 29, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Arnold L. Brown, M.D., Chair
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D.
Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Meryl H. Karol, Ph.D.*
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D.
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D., M.S., Principal Reviewer
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.*
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D., Principal Reviewer
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D.
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Mary Jo Vodicnik, Ph.D.*
Lilly MSG Development Center
Belgium

Jerrold M. Ward, D.V.M., Ph.D.
National Cancer Institute
Frederick, MD

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 29, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol by discussing the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms in rats and mice and possible compound-related nonneoplastic lesions in rats and female mice. The proposed conclusions for the studies were *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in male and female F344/N rats and B6C3F$_1$ mice.

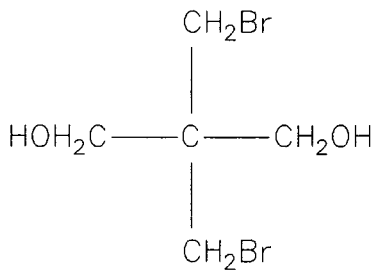
Dr. Russo, a principal reviewer, agreed with the proposed conclusions. She asked if there was more information on possible mutagenic or carcinogenic effects of the impurities detected in the compound or on the metabolism of 2,2-bis(bromomethyl)-1,3-propanediol and its contaminants. (The studies were conducted on commercially available fire retardant from the sole manufacturer, and no attempt was made to study impurities, contaminants, or metabolites.)

Dr. Ryan, the second principal reviewer, agreed with proposed conclusions. She questioned the rationale for dosed feed administration since the text suggested dermal and inhalation exposures were the most likely exposure routes for humans. Dr. Dunnick said the oral route was chosen to provide maximum exposure to the tissues. Dr. Ryan remarked on the large differences between the overall and adjusted incidence rates for several neoplasms and asked for discussion as to why. Dr. J.K. Haseman, NIEHS, said the adjusted rate provides an estimate of overall neoplasm incidence if all animals survive to the end of the study. In many cases this adjusted rate is reasonable, but it is less meaningful when there are only a few survivors as in the high dose groups of rats in the 2,2-bis(bromomethyl)-1,3-propanediol study.

Dr. Miller, the third principal reviewer, agreed with the proposed conclusions. She asked how the rodent doses would compare with likely human exposures and suggested that information be added as to the sources, routes, and degrees of human exposure. Dr. Dunnick responded that the one company that produces 2,2-bis(bromomethyl)-1,3-propanediol had not published information on worker exposure but noted that the Environmental Protection Agency has requested such information. Dr. J. Haartz, NIOSH, added that no information on 2,2-bis(bromomethyl)-1,3-propanediol was found in the National Occupational Exposure Survey, so there was no estimate of potentially exposed workers. Dr. Miller asked whether there should be concerns with vapor or pyrolysis products in the event of a fire. Dr. Dunnick said the chemical volatilizes at temperatures greater than 200° C and at high temperatures would form hydrogen bromide.

Dr. Miller moved that the technical report on 2,2-bis(bromomethyl)-1,3-propanediol be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *clear evidence of carcinogenic activity*. Dr. Ryan seconded the motion, which was accepted unanimously with seven votes.

INTRODUCTION



2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL (FR-1138®)

(Technical Grade: 78.6% 2,2-bis(bromomethyl)-1,3-propanediol, 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane, 6.9% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane, 0.2% pentaerythritol, and 7.7% dimers and structural isomers)

CAS No. 3296-90-0

Chemical Formula: $C_5H_{10}Br_2O_2$ Molecular Weight: 261.94

Synonyms: 2,2-Bis(2-bromomethyl)-1,3-propanediol; 1,3-dibromo-2,2-dihydroxymethylpropane; 1,3-dibromo-2,2-dimethylolpropane; 2,2-dibromomethyl-1,3-propanediol; dibromopentaerythritol; dibromoneopentyl glycol; pentaerythritol dibromide; pentaerythritol dibromohydrin

CHEMICAL AND PHYSICAL PROPERTIES

2,2-Bis(bromomethyl)-1,3-propanediol is a white solid material with a slight, mild, musty odor. It has a melting point of 75° to 95° C for technical grade material and 109° to 110° C for pure material. It is soluble in acetone, ethanol, and ether, and slightly soluble in water (2 g/1,000 g water at 25° C). The material is produced by replacement of the hydroxyl groups of pentaerythritol with bromide. In the case of 2,2-bis(bromomethyl)-1,3-propanediol approximately one-half of the hydroxyl groups of pentaerythritol are replaced with bromine-bonded carbon atoms. The compound is unique in that the aliphatic neopentyl structure contains no hydrogen atoms on the carbon atom adjacent to the carbon bonded to the bromine. This provides a compound very resistant to dehydrobromination by elevated temperatures, by chemical reactions, or by photodegradation. The remaining hydroxyl groups provide reactive sites that allow for polymerization. These hydroxyl groups readily react with organic acids to form esters, with isocyanates to form urethanes, or with epoxides to form ethers. In addition, 2,2-bis(bromomethyl)-1,3-propanediol can react with aldehydes and ketones to form cyclic acetals or ketals, or with phosphorous oxyhalides to form cyclic phosphates or phosphites (Larsen, 1969; Larsen and Weaver, 1973).

USE AND HUMAN EXPOSURE

2,2-Bis(bromomethyl)-1,3-propanediol is used as a flame retardant in unsaturated polyester resins, for molded products, and in rigid polyurethane foam. This flame retardant may enter the environment as fugitive dust and through wastewater. 2,2-Bis(bromomethyl)-1,3-propanediol is expected to remain for long periods of time in water (USEPA, 1983).

It is estimated that three to four million pounds of 2,2-bis(bromomethyl)-1,3-propanediol are produced per year (USEPA, 1983), but current production figures are not reported (USITC, 1994). The United States produces 65% of the world's bromine, and the major uses for bromine in the United States are manufacturing of lead scavengers in gasoline (48%), flame retardants (29%), sanitation preparations (16%), and other uses (6%). The demand for bromine-based flame retardant chemicals has increased (Margler, 1982).

The brominated flame retardants (including FR-1138®) are a use-based class of 22 chemicals recommended by the United States Environmental Protection Agency for additional study (*Fed. Regist.*, 1989, 1990) but were withdrawn from testing in 1994 because of the availability of sufficient toxicity data or limited production or use in the United States (*Fed. Regist.*, 1994).

The National Institute for Occupational Safety and Health did not survey any United States facilities for 2,2-bis(bromomethyl)-1,3-propanediol exposure information (NIOSH, 1995).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

The National Institute of Environmental Health Sciences has ongoing studies on the absorption, distribution, metabolism, and excretion of 2,2-bis(bromomethyl)-1,3-propanediol in rodents. However, there are no published studies on the metabolism of 2,2-bis(bromomethyl)-1,3-propanediol.

Humans

No information on the absorption, distribution, metabolism, and excretion of 2,2-bis(bromomethyl)-1,3-propanediol in humans was found in a search of the available literature.

TOXICITY

Experimental Animals

The oral LD_{50} of 2,2-bis(bromomethyl)-1,3-propanediol in male rats is reported to be 3,458 mg/kg (range 2,810 to 4,257 mg/kg; Keyes *et al.*, 1979). A comparison of the toxicity of 2,2-bis(bromomethyl)-1,3-propanediol in rats and mice by the dosed feed and gavage administration demonstrated similar effects by each route at comparable doses (Elwell *et al.*, 1989). The results of the feed studies are provided in this report.

Humans

No information on 2,2-bis(bromomethyl)-1,3-propanediol toxicity in humans has been reported in the literature.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

The effect of 2,2-bis(bromomethyl)-1,3-propanediol on reproduction in Swiss (CD-1®) mice was evaluated by administering 2,2-bis(bromomethyl)-1,3-propanediol in feed at 1,000, 2,000, or 4,000 ppm in a continuous breeding study in which male and female F_0 mice were exposed 7 days prior to and during a 98-day cohabitation period (Morrissey *et al.*, 1989; Treinen *et al.*, 1989). Although the fertility index was unchanged, 2,2-bis(bromomethyl)-1,3-propanediol exposure caused significantly decreased numbers of litters per pair, pups born alive per litter, and pup weight in mice exposed to 4,000 ppm. Sperm concentration, motility, morphology, and estrual cyclicity were unaffected by treatment. Crossover mating between exposed (4,000 ppm) and control F_0 mice indicated a specific effect on the female reproductive capacity. A decrease in the number of live pups per litter and decrease in pup weight were seen when exposed females were mated to control males but not when exposed males were mated to control females. 2,2-Bis(bromomethyl)-1,3-propanediol at 4,000 ppm caused generalized toxicity in males and females as evidenced by the lower body weight, and this generalized toxicity may have contributed, in part, to the reproductive impairment produced by 2,2-bis(bromomethyl)-1,3-propanediol at the 4,000 ppm concentration.

Humans

No information on the reproductive and developmental toxicity of 2,2-bis(bromomethyl)-1,3-propanediol in humans has been reported in the literature.

CARCINOGENICITY

Experimental Animals

In a 2-year toxicity/carcinogenicity study, Sprague-Dawley rats were administered the flame retardant 2,2-bis(bromomethyl)-1,3-propanediol [FR-1138®: 80% dibromopentyl glycol (2,2-bis(bromomethyl)-1,3-propanediol); 8% tribromoneopentyl alcohol (bis(bromomethyl)-1-bromo-3-hydroxypropane) and 6% monobromoneopentyl triol (2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane)] in feed at concentrations that delivered 0, 5, or 100 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight per day (Keyes *et al.*, 1979). No carcinogenic effect was observed. However, degenerative changes in the liver and lens of the eye were attributed to chemical exposure. The article did not provide details on the preparation or stability of the chemical in the feed. No dose-related effects on the feed consumption, weight gain, clinical signs, or mortality were observed, suggesting that the animals may have been able to tolerate higher doses.

Humans

No information on the carcinogenic potential of 2,2-bis(bromomethyl)-1,3-propanediol in humans has been reported in the literature.

GENETIC TOXICITY

There are no mutagenicity data for 2,2-bis(bromomethyl)-1,3-propanediol other than the NTP studies included in Appendix E of this report. These data indicate that 2,2-bis(bromomethyl)-1,3-propanediol is mutagenic, but that specific conditions are required to observe a positive response. 2,2-Bis(bromomethyl)-1,3-propanediol was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of 30% induced hamster liver S9 (Zeiger *et al.*, 1992); in the presence of 30% rat liver S9, no mutagenic response was observed. An earlier *Salmonella* mutation study showed no mutagenicity in strains TA98, TA100, TA1535, or TA1537 with or without 10% induced hamster or rat liver S9 (Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary cells (Galloway *et al.*, 1987), 2,2-bis(bromomethyl)-1,3-propanediol induced a dose-related increase in chromosomal aberrations in the presence of induced rat liver S9; no increase in sister chromatid exchange frequency was noted in cultured Chinese hamster ovary cells treated with 2,2-bis(bromomethyl)-1,3-propanediol, with or without S9.

STUDY RATIONALE

The National Cancer Institute nominated the flame retardant 2,2-bis(bromomethyl)-1,3-propanediol [FR-1138®: 80% dibromopentyl glycol (2,2-bis(bromomethyl)-1,3-propanediol); 8% tribromoneopentyl alcohol (bis(bromomethyl)-1-bromo-3-hydroxypropane) and 6% monobromoneopentyl triol (2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane)] for study because it is a widely used flame retardant, and there was little or no information on the toxicity or carcinogenicity of this flame retardant reported in the literature at the time of nomination for study.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

2,2-Bis(bromomethyl)-1,3-propanediol was obtained from Dow Chemical Company (Rolling Meadows, IL) in one lot (840429-162) which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix I). Reports on analyses performed in support of the 2,2-bis(bromomethyl)-1,3-propanediol studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a fine white powder, was identified as 2,2-bis(bromomethyl)-1,3-propanediol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values for 2,2-bis(bromomethyl)-1,3-propanediol. Karl Fischer water analysis indicated 0.3% ± 0.1% water. Thin-layer chromatography by two systems indicated a major spot and one impurity. Gas chromatography using one system indicated one major peak and three impurities, and a second system indicated a major peak and four impurities. In both cases, the total impurity peak area was less than 3%. High-performance liquid chromatography analyses detected multiple impurities with five impurity peaks having areas of 1% or greater relative to the major peak area. The overall impurity peak area was 21.2%. Four impurities were isolated for identification by mass spectrometry. Two impurities, 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%) and 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane (6.9%), were identified. One impurity (1%) was tentatively identified as a dimer of the parent chemical. Another impurity peak (2.8%) consisted of multiple components, including a structural isomer and a dimer of the major component. A quantitative analysis for pentaerythritol, a reactant in the synthesis of 2,2-bis(bromomethyl)-1,3-propanediol, was also conducted. Using a reference standard, 0.2% pentaerythritol was found. The overall purity for lot 840429-162 was determined to be approximately 79%.

Stability studies, performed by the analytical chemistry laboratory using gas chromatography, found that 2,2-bis(bromomethyl)-1,3-propanediol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in sealed containers protected from light. Stability was monitored monthly during the 13-week and 2-year studies using gas chromatography. No degradation of bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared weekly by mixing 2,2-bis(bromomethyl)-1,3-propanediol with feed (Table I1). Homogeneity and stability studies were performed by the analytical chemistry laboratory using gas chromatography. Homogeneity was confirmed, and the stability of the dose formulations was confirmed for at least 3 weeks when stored in the dark at −20° C. During the 13-week and 2-year studies the dose formulations were stored in the dark at −20° C for no more than 3 weeks.

Periodic analyses of the dose formulations of 2,2-bis(bromomethyl)-1,3-propanediol were conducted at the study laboratory and analytical chemistry laboratory using gas chromatography. During the 13-week studies, dose formulations were analyzed at the beginning, midpoint, and end of the studies (Table I2). During the 2-year studies, dose formulations were analyzed at least every 10 weeks (Table I3). Of the dose formulations analyzed, 92% (119/130) were within 10% of the target concentration. Results of periodic referee analyses performed

by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 2,2-bis(bromomethyl)-1,3-propanediol and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the rats and mice were 4 weeks old. The animals were quarantined for 11 (mice) or 14 (rats) days and were 6 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and two male and four female control mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

The concentrations for these 13-week feed studies were based on previous 13-week gavage studies where the chemical was administered to F344/N rats at doses of 0, 50, 100, 200, 400, or 800 mg/kg and to B6C3F$_1$ mice at doses of 0, 25, 50, 100, 200, or 400 mg/kg (Elwell *et al.*, 1989). Decreased body weights, urinary bladder transitional cell hyperplasia, and kidney degeneration occurred in male rats receiving 800 mg/kg, and male and female mice receiving 200 or 400 mg/kg. Body weights of female rats receiving 800 mg/kg were only marginally decreased. A high dose of 20,000 ppm was selected for the rat feed study which was estimated to deliver approximately 1,000 mg/kg. The high dose selected for the mouse feed study was 10,000 ppm which was estimated to deliver approximately 4,000 mg/kg. The doses for the 13-week mouse feed study were also selected to allow overlapping doses with the rat study for comparison of species response to 2,2-bis(bromomethyl)-1,3-propanediol.

Groups of 10 male and 10 female rats received 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 13 weeks. Groups of 10 male and 10 female mice received 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 13 weeks. Feed and water were available *ad libitum* except during urine collections. Rats were housed five per cage and mice were housed individually. Clinical findings were recorded weekly for rats and mice. Feed consumption was recorded weekly by cage. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Clinical pathology studies were performed on all male and female rats and mice in the 13-week studies. Selected serum chemistry parameters were measured on days 3, 15, 30, 60, and week 13 on rats in a special study group and at week 13 on rats and mice in the core studies. Urinalysis studies were performed on days 3, 15, 30, 60, and week 13 on rats in the special study group and at week 13 on rats and mice in the core studies. Urinalysis water deprivation studies were conducted on days 4, 16, 31, 61, and week 13 on rats in the special study group.

For serum chemistry studies, rats and mice were anesthetized with carbon dioxide and bled from the retroorbital sinus. Blood for serum analyses was collected in containers without anticoagulant, allowed to clot at room temperature, and centrifuged to separate the serum. For all urine studies, rats and mice were placed individually into metabolism cages for 16-hour (rats) or 24-hour (mice) urine collection. The urine containers were kept immersed in an ice water bath during sampling to minimize evaporation and suppress bacterial growth. During urine collection periods feed was removed and, except for during water deprivation studies, water was available *ad libitum*. For water deprivation studies, urine was collected from special study rats for 4 hours following a 16-hour water deprivation period. Water deprivation began approximately 8 hours after the blood collection required for serum chemistry analyses. Serum and urine chemistry end points were determined on a Cobas Fara chemistry analyzer (Roche Diagnostics Systems, Inc., Montclair, NJ) using reagents and methods obtained from the manufacturer. Urine volume was determined volumetrically and urine specific gravity was determined by refractometry. Parameters evaluated are listed in Table 1.

At the end of the studies, samples from 0, 5,000, 10,000, and 20,000 ppm rats and 0, 2,500, 5,000, and 10,000 ppm mice were collected for sperm morphology and vaginal cytology evaluations. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP General Statement of Work (April, 1984). For 7 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and aspirated samples of vaginal fluid and cells were transferred to slides and stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). All males were evaluated for sperm morphology, count, and motility. The right testis and right epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each right cauda epididymis was placed in buffered saline solution and finely minced. The tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemocytometer. To quantify spermatogenesis, testicular spermatid head count was determined in the left testis by removing the tunica albuginea and homogenizing the testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted.

A necropsy was performed on all animals surviving to the end of the studies. The brain, heart, right kidney, liver, lung, spleen, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on control rats and mice, 20,000 ppm rats, and 10,000 ppm mice. In addition, the kidneys and urinary bladder of all other dose groups of rats and mice were examined. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats received 2,500, 5,000, or 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Groups of 70 male and 60 female rats received 0 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Groups of 60 male and 60 female mice received 0, 312, 625, or 1,250 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 104 to 105 weeks. Up to 10 male and female rats and mice from each group were evaluated at 15 months.

Stop-Exposure Evaluation

A group of 70 male rats received 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 3 months, when ten control and ten 20,000 ppm rats were evaluated. At 3 months, the dosed feed was replaced with a control diet for the remainder of the study.

Source and Specification of Animals

Male and female F344/N rats and B6C3F_1 mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. On receipt, the animals were approximately 4 weeks old. The animals were quarantined for 10 to 12 days and were 6 weeks old on the first day of the studies. Before the initiation of the studies, 10 male and 10 female rats and five male and five female mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats were housed five per cage and mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured every 4 weeks by cage. Cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on

feed composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded initially, weekly for 13 weeks, monthly thereafter, and at the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice except one 1,250 ppm male mouse that was missing. At the 3-month (male rats) and 15-month interim evaluations, the right kidney and liver of rats and mice were weighed. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the esophagus, kidney, pharynx, thyroid gland, tongue, and Zymbal's gland of male and female rats to confirm the incidences of neoplasms and nonneoplastic lesions. In addition, for male rats, the quality assessment pathologist reviewed ear, eye, forestomach, large and small intestine, liver, pancreas, seminal vesicle/coagulative gland, skin, spleen, teeth, urinary bladder, and multiple organs (mesothelioma) to confirm the incidences of neoplasms and nonneoplastic lesions. For mice, the quality assessment pathologist reviewed the forestomach, harderian gland, and lung of all mice to confirm the incidences of neoplasms and nonneoplastic lesions.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and any other tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 are given as the number of animals bearing

such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the number of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

In these studies, large numbers of exposed rats died or were killed moribund early in the studies. These deaths were considered to be due primarily to Zymbal's gland neoplasms, subcutaneous tumors, and mononuclear cell leukemia. Consequently, for these particular lesions, primary emphasis in the analysis of neoplasm incidence was given to the life table test (Cox, 1972; Tarone, 1975), a survival-adjusted procedure appropriate for rapidly lethal neoplasms. For incidental neoplasms, the statistical method used was a logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984). Other statistical analyses reported in the appendixes include the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures that are based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry, urinalysis, spermatid, and epididymal spermatozoa data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973). Because the vaginal cytology data are proportions (the proportion of the observation period that

an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of 2,2-bis(bromomethyl)-1,3-propanediol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and the frequency of micronucleated erythrocytes in peripheral blood and bone marrow. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of 2,2-bis(bromomethyl)-1,3-propanediol are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

13-Week Studies	2-Year Studies
Study Laboratory	
American Biogenics Corporation (Woburn, MA)	Southern Research Institute (Birmingham, AL)
Strain and Species	
Rats: F344/N	Rats: F344/N
Mice: $B6C3F_1$	Mice: $B6C3F_1$
Animal Source	
Taconic Farms (Germantown, NY)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies	
Rats: 14 days	Rats: 10 or 11 days
Special Clinical Chemistry and Urinalysis Study (rats only):	Mice: 12 days
13-15 days (males)	
20-22 days (females)	
Mice: 11 days	
Average Age When Studies Began	
6-7 weeks	6 weeks
Date of First Dose	
Rats: 22 April 1986	Rats: 27 March 1989
Special Clinical Chemistry and Urinalysis Study (rats only):	Mice: 13 March 1989
12-14 May 1986 (males)	
19-21 May 1986 (females)	
Mice: 14 April 1986	
Duration of Dosing	
13 weeks	104 to 105 weeks
Date of Last Dose	
Rats: 22-24 July 1986	Rats: 24 March 1991 (males)
Special Clinical Chemistry and Urinalysis Study (rats only):	26 March 1991 (females)
13-15 August 1986 (males)	Mice: 10 March 1991 (males)
21-22 August 1986 (females)	17 March 1991 (females)
Mice: 14-16 July 1986	
Necropsy Dates	
Rats: 22-24 July 1986	Rats: 3-month interim evaluation - 26 June 1989
Special Clinical Chemistry and Urinalysis Study (rats only):	15-month interim evaluation - 25 June 1990
13-15 August 1986 (males)	terminal sacrifice - 1-5 April 1991
21-22 August 1986 (females)	Mice: 18-26 March 1991
Mice: 14-16 July 1986	
Age at Necropsy	
Rats: 19-20 weeks	Rats: 111 weeks
Mice: 19 weeks	Mice: 111-112 weeks

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

13-Week Studies	2-Year Studies
Size of Study Groups	
10 males and 10 females	Rats: 60 males and 60 females (2,500, 5,000, and 10,000 ppm); 70 males and 60 females (0 ppm); 70 males (20,000 ppm stop-exposure) Mice: 60 males and 60 females
Method of Distribution	
Randomized by weight into cage groups using a computer-generated table of random numbers	Randomized by weight using a random number table
Animals per Cage	
Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification	
Toe clip	Rats: Tail tattoo Mice: Toe clip
Diet	
NIH-07 open formula mash diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 13-week studies
Water Distribution	
Tap water (Woburn, MA, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI, or Hardco, Cincinnati, OH) available *ad libitum*, except during urine collection	Tap water (Birmingham, AL, municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI) available *ad libitum*
Cages	
Polycarbonate (Lab Products Inc., Garfield, NJ), changed twice weekly	Same as 13-week studies, except mouse cages were changed weekly
Bedding	
Sani-Chip (P.J. Murphy Forestry Products, Corp., Rochelle Park, NJ)	Same as 13-week studies
Cage Filters	
Non-woven filter sheets	Reemay® spun-bonded polyester (Andico, Birmingham, AL) changed every 2 weeks
Racks	
Stainless steel (Lab Products Inc., Garfield, NJ), changed once every 2 weeks	Same as 13-week studies
Animal Room Environment	
Temperature: 18° to 26° C Relative humidity: 48% to 75% Fluorescent light: 12 hours/day Room air: 12 changes per hour	Temperature: 19° to 29° C (rats); 14° to 25° C (mice) Relative humidity: 26.3% to 90% (rats); 25.5% to 85.3% (mice) Fluorescent light: 12 hours/day Room air: 10 changes per hour

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

13-Week Studies	2-Year Studies
Doses	
Rats: 0, 1,250, 2,500, 5,000, 10,000 or 20,000 ppm in feed, available *ad libitum* Mice: 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm in feed, available *ad libitum*	Rats: continuous-exposure study - 0, 2,500, 5,000, or 10,000 ppm; stop-exposure study - 20,000 ppm in feed, available *ad libitum* Mice: 0, 312, 625, or 1,250 ppm in feed, available *ad libitum*
Type and Frequency of Observation	
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical observations were recorded weekly. Feed consumption was measured weekly by cage.	Observed twice daily; body weights and clinical observations recorded initially, weekly for weeks 2 to 13, monthly thereafter, and at the end of the studies. Feed consumption was measured every 4 weeks by cage.
Method of Sacrifice	
Anesthetized with CO_2 followed by exsanguination via orbital bleeding	Same as 13-week studies
Necropsy	
Necropsy performed on all animals surviving to the end of the study. Organs weighed included the brain, heart, right kidney, liver, lung, spleen, right testis, and thymus.	All animals (except one 1,250 ppm mouse) were necropsied. Organs weighed at the 3-month (control and stop-exposure male rats) and 15-month interim evaluations were the right kidney and liver.
Clinical Pathology	
At the end of the 13-week studies, blood was collected from the retro-orbital sinus and urine was collected from all rats and mice. In the special study rats, blood was collected on days 3, 15, 30, 60, and at study termination. Urine samples were collected on days 3, 15, 30, 60, and at study termination. Additional urine samples were collected for measurement of urinary concentrating ability following 16-hour water deprivation periods. ***Clinical Chemistry:*** albumin, albumin/globulin ratio, creatinine (rats only), globulin, glucose, total protein, and urea nitrogen ***Urinalysis:*** glucose, protein, specific gravity, and volume	None
Sperm and Vaginal Cytology Evaluation	
Sperm and vaginal fluid samples were evaluated in 0, 5,000, 10,000, and 20,000 ppm rats and 0, 2,500, 5,000, and 10,000 ppm mice at the end of the studies. The parameters evaluated in males were sperm count, morphology, and motility. The right cauda, right epididymis, and right testis were weighed. Vaginal fluid samples were collected for up to 7 consecutive days prior to the end of the studies for vaginal cytology evaluations. The parameters evaluated in females were relative frequency of estrous stages and estrous cycle length.	None

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

13-Week Studies	2-Year Studies
Histopathology	
Complete histopathologic examinations were performed on all control rats and mice, 20,000 ppm rats, and 10,000 ppm mice. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular or mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland (rats), prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, and ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney and urinary bladder of all other rats and mice were also examined.	Complete histopathologic examinations were performed on all animals necropsied. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), liver, lung, lymph nodes (mandibular or mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, and ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

13-WEEK STUDY

All rats survived to the end of the study (Table 2). The final mean body weights and weight gains of 5,000, 10,000, and 20,000 ppm males and females were significantly lower than those of the controls. Feed consumption by exposed animals was lower than that by controls at week 1, but was generally similar to or slightly higher than that by controls at week 13 (Table 2). Dietary levels of 1,250, 2,500, 5,000, 10,000, and 20,000 ppm delivered average daily doses of 100, 200, 400, 800, and 1,700 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight to males, and 100, 200, 400, 800, and 1,630 mg/kg to females. No chemical-related clinical findings were observed.

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	115 ± 3	353 ± 6	238 ± 4		16.1	17.9
1,250	10/10	116 ± 4	354 ± 6	238 ± 5	100	15.5	19.2
2,500	10/10	114 ± 3	338 ± 5	224 ± 4*	96	15.0	18.1
5,000	10/10	117 ± 4	324 ± 7**	207 ± 7**	92	15.0	19.3
10,000	10/10	116 ± 5	314 ± 6**	198 ± 4**	89	14.3	20.0
20,000	10/10	120 ± 5	269 ± 4**	149 ± 5**	76	13.7	19.3
Female							
0	10/10	96 ± 3	209 ± 4	113 ± 2		11.6	11.9
1,250	10/10	100 ± 2	204 ± 3	105 ± 2*	98	11.5	13.0
2,500	10/10	99 ± 3	200 ± 3	101 ± 1**	96	11.4	11.8
5,000	10/10	93 ± 2	196 ± 3**	102 ± 2**	94	11.4	12.2
10,000	10/10	97 ± 2	191 ± 3**	94 ± 3**	92	11.4	12.1
20,000	10/10	95 ± 2	174 ± 3**	79 ± 2**	83	10.3	11.6

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.

Urinalysis and clinical chemistry data for rats in the core study are listed in Table G1. At the end of the study, 16-hour urine volumes in 10,000 and 20,000 ppm male rats were two-fold greater than that in the control group. These higher urine volumes were accompanied by urine specific gravity which was lower than that in the control group. Urine specific gravity in the 5,000 ppm male group was also lower than that in the control group. The female rats were less affected; minimal differences in the urine volume and specific gravity occurred only in the 2,500 ppm group. Renal papillary degeneration occurred in male rats exposed to 5,000 ppm or greater, which would be consistent with the increase in urine volume (polyuria). Minimally increased urine protein excretion (proteinuria) also occurred in the 10,000 and 20,000 ppm groups and may have been related to the renal lesions. In female rats, renal papillary degeneration was present in only one animal in the 20,000 ppm group and could explain the lack of polyuria or proteinuria in females.

Serum total protein and albumin concentration in female rats exposed to 2,500 ppm or greater were slightly lower than those in the controls. Decreased protein values can be caused by several factors including hyperhydration, albumin and/or protein loss associated with renal or intestinal disease (Kaneko, 1989; Nguyen, 1989).

No biologically significant differences in organ weights were observed (Table F1).

There were no treatment-related gross lesions. Treatment-related microscopic lesions were present in the kidney of male and female rats and the urinary bladder of male rats (Table 3). A minimal to mild degeneration of the renal papilla was present in 5,000, 10,000, and 20,000 ppm male rats and in one female rat in the 20,000 ppm group. This degenerative change was characterized by edema of the interstitial tissue at the distal tip of the renal papilla. The interstitial cells of the renal papilla appeared swollen and the nuclei stained less distinctly than in the controls. In the areas of papillary degeneration, there was increased eosinophilic staining of the cytoplasm of the interstitial cells that contained PAS-positive droplets. The cytoplasm of the epithelial cells lining the collecting ducts was vacuolated, and frequently a clear, nonstaining area in the cytoplasm was present around the nuclei of these cells. In the urinary bladder of male rats in the 20,000 ppm group, there was minimal hyperplasia of the transitional epithelium.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Kidney[a]	10	10	10	10	10	10
Degeneration, Papillary[b]	0	0	0	3 (1.0)[c]	6** (1.3)	8** (1.3)
Urinary Bladder	10	10	10	10	10	10
Hyperplasia	0	0	0	0	0	9** (1.0)
Female						
Kidney	10	10	10	10	10	10
Degeneration, Papillary	0	0	0	0	0	1 (1.0)

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected rats: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Clinical Chemistry and Urinalysis in Special Study Rats

Urinalysis and clinical chemistry data for rats in the special study are listed in Table G1. Similar to the core study animals, changes in urine volume and specific gravity were the major treatment effects, and male rats were more affected than females. On days 3 and 15, urine volume was slightly decreased, and urine specific gravity was increased in 20,000 ppm males compared to controls. On day 3, urine volume was also slightly decreased in the 20,000 ppm females. This would be consistent with a mild transient dehydration related to decreased food and water intake resulting in a smaller, but more concentrated, urine volume. Transient dehydration is supported by the mild increase in serum total protein concentration that occurred in a treatment-related fashion in male rats on days 3 and 15. By day 60, urine volumes were markedly increased (polyuria) in 10,000 and 20,000 ppm males compared to that of the controls. At this time, urine specific gravity decreased to the isosthenuric range (1.008 to 1.012) in these animals and in 5,000 ppm male rats. Additionally, a decreased urine specific gravity occurred in females exposed to 2,500 ppm or greater but was not accompanied by increased urine volume. At the end of the study, 16-hour urine volume was increased in the 20,000 ppm males and was accompanied by decreased urine specific gravity in 10,000 and 20,000 ppm males and 5,000 ppm females. Water deprivation tests demonstrated that male and female rats were able to adequately concentrate their urine in response to dehydration throughout the study. However, by day 61 the urine specific gravity in water-deprived, 20,000 ppm males was lower than that in the control group. Renal papillary degeneration that occurred in males exposed to 5,000 ppm or greater would be consistent with isosthenuric polyuria. On day 61, a minimal increase in the urine protein excretion also occurred in 10,000 and 20,000 ppm males and could be consistent with renal lesions. By day 60, an increase in serum total protein concentration occurred in 5,000 and 20,000 ppm male rats. This could be consistent with excess renal fluid loss resulting in a mild dehydration. Again, the absence of renal papillary degeneration in female rats could explain the lack of polyuria. Changes in other clinical chemistry and urinalysis variables were minor, sporadic, and were not considered relevant.

Dose Selection Rationale: Based on lower final mean body weights in the 20,000 ppm males and females, the incidences of renal papillary degeneration in 20,000 ppm males and females, and hyperplasia of the urinary bladder in 20,000 ppm males, the high dose selected for continuous exposure in the 2-year study was 10,000 ppm; 20,000 ppm was selected as the exposure concentration for a 3-month stop-exposure study in male rats to evaluate the potential for progression or regression of urinary bladder and kidney lesions.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 4 and in the Kaplan-Meier survival curves in Figure 1. Survival of 5,000 and 10,000 ppm continuous-exposure males and females and 20,000 ppm stop-exposure males was significantly lower than that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of males and females receiving 10,000 ppm and stop-exposure males receiving 20,000 ppm were lower than those of the controls throughout most of the study (Tables 5 and 6 and Figure 2). In the continuous-exposure study, feed consumption by exposed rats was generally similar to that by the controls throughout the study (Tables J1 and J2). In 20,000 ppm stop-exposure males the feed consumption was lower than that by controls. Dietary levels of 2,500, 5,000, and 10,000 ppm delivered average daily doses of 100, 200, and 430 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight to males and 115, 230, and 460 mg/kg to females. Dietary levels of 20,000 ppm delivered an average daily dose of 800 mg/kg to stop-exposure males. Clinical findings included skin and subcutaneous tissue masses on the face, tail, and the ventral and dorsal surfaces of exposed rats.

TABLE 4
Survival of Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
Animals initially in study	70	60	60	60	70
3-Month interim evaluation[b]	10	0	0	0	10
15-Month interim evaluation[b]	9	7	9	5	0
Moribund	24	30	36	43	55
Natural deaths	1	3	2	11	5
Animals surviving to study termination	26	20	13	1	0
Percent probability of survival at the end of study[c]	51	38	26	2	0
Mean survival (days)[d]	688	652	669	587	544
Survival analysis[e]	P<0.001	P=0.126	P=0.010	P<0.001	P<0.001
Female					
Animals initially in study	60	60	60	60	
15-Month interim evaluation[b]	10	9	7	8	
Moribund	14	22	27	41	
Natural deaths	0	2	3	6	
Animals surviving to study termination	36	27	23	5	
Percent probability of survival at the end of study	72	53	43	10	
Mean survival (days)	711	701	676	630	
Survival analysis	P<0.001	P=0.095	P=0.005	P<0.001	

a Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats received control feed until the end of the 2-year study.
b Censored from survival analyses
c Kaplan-Meier determinations
d Mean of all deaths (uncensored, censored, and terminal sacrifice).
e The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

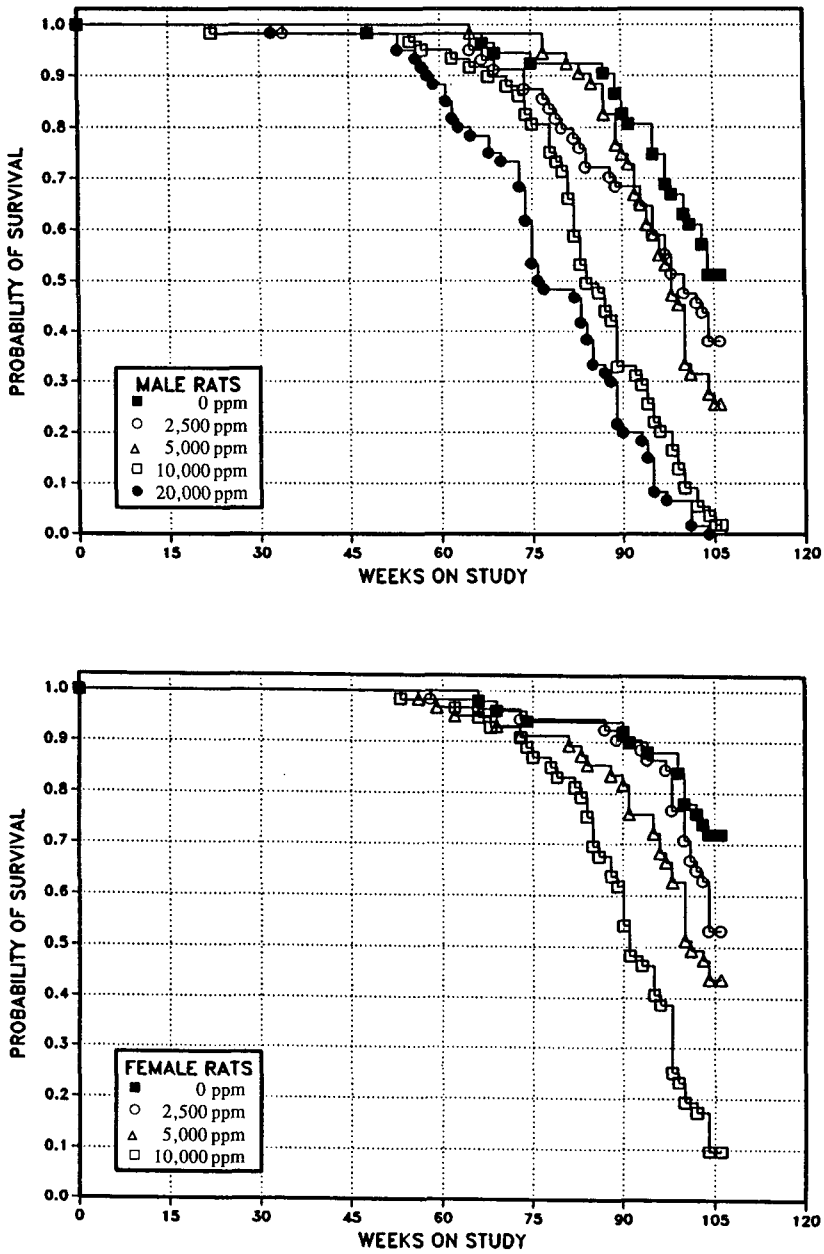


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Weeks on Study	0 ppm		2,500 ppm			5,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	114	70	114	101	60	114	100	60
2	163	70	161	99	60	157	97	60
3	198	70	195	99	60	193	98	60
4	231	70	227	98	60	223	97	60
5	249	70	242	98	60	236	95	60
6	267	70	260	98	60	253	95	60
7	284	70	277	98	60	269	95	60
8	295	70	288	98	60	285	97	60
9	306	70	297	97	60	291	95	60
10	314	70	306	97	60	300	96	60
11	321	70	311	97	60	305	95	60
12	330	70	323	98	60	316	96	60
13	341	70	333	98	60	326	96	60
17[a]	365	60	355	97	60	346	95	60
21	386	60	374	97	60	362	94	60
25	399	60	386	97	60	376	94	60
29	412	60	401	97	60	384	93	60
33	424	60	413	97	60	401	95	60
37	432	60	423	98	59	412	95	60
41	442	60	431	97	59	424	96	60
45	440	60	432	98	59	420	96	60
49	452	59	438	97	59	430	95	60
53	454	59	444	98	59	438	96	60
57	458	59	454	99	59	446	97	60
61	461	59	452	98	59	438	95	60
65	463	59	449	97	58	445	96	60
69[a]	457	49	449	98	49	443	97	50
73	455	48	446	98	48	435	96	50
77	450	47	443	98	46	431	96	50
81	444	47	442	100	42	428	96	48
85	443	47	442	100	38	428	97	46
89	440	44	440	100	37	418	95	42
93	435	41	429	99	35	412	95	33
97	432	35	433	100	29	403	93	27
101	432	31	426	99	25	408	94	16
105	425	26	425	100	20	401	95	13
Mean for weeks								
1-13	263		256	97		251	95	
14-52	417		406	97		395	95	
53-105	446		441	99		427	96	

(continued)

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Weeks on Study	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 ppm No. of Survivors	20,000 ppm[b] Av. Wt. (g)	20,000 ppm[b] Wt. (% of controls)	20,000 ppm[b] No. of Survivors
1	109	96	60	105	93	70
2	152	94	60	134	83	70
3	181	91	60	157	79	70
4	208	90	60	176	76	70
5	221	89	60	185	74	70
6	236	89	60	197	74	70
7	249	88	60	206	73	70
8	259	88	60	215	73	70
9	264	86	60	218	71	70
10	273	87	60	222	71	70
11	279	87	60	229	72	70
12	288	87	60	238	72	70
13	298	88	60	245	72	70
17[a]	319	88	60	292	80	60
21	340	88	60	323	84	60
25	355	89	59	347	87	60
29	367	89	59	366	89	60
33	377	89	59	382	90	59
37	388	90	59	399	92	59
41	396	90	59	410	93	59
45	395	90	59	410	93	59
49	401	89	59	419	93	59
53	414	91	59	430	95	57
57	418	91	57	431	94	56
61	415	90	57	422	92	53
65	414	89	56	429	93	48
69[a]	420	92	49	430	94	45
73	406	89	48	423	93	44
77	416	92	44	424	94	30
81	407	92	39	414	93	29
85	402	91	27	410	93	22
89	394	89	20	409	93	15
93	388	89	16	374	86	11
97	384	89	11	402	93	5
101	369	86	5	373	86	3
105						
Mean for weeks						
1-13	232	88		194	74	
14-52	371	89		372	89	
53-105	404	91		413	93	

[a] Interim evaluations occurred during week 14 (0 and 20,000 ppm groups) and week 66 (0, 2,500, 5,000, and 10,000 ppm groups).
[b] Stop-exposure group

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors	5,000 ppm Av. Wt. (g)	5,000 ppm Wt. (% of controls)	5,000 ppm No. of Survivors	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 ppm No. of Survivors
1	106	60	105	99	60	106	100	60	106	100	60
2	130	60	127	98	60	126	98	60	127	98	60
3	144	60	142	99	60	139	97	60	138	96	60
4	154	60	151	98	60	150	97	60	147	96	60
5	161	60	159	99	60	156	97	60	152	95	60
6	168	60	165	98	60	165	98	60	159	95	60
7	175	60	172	98	60	171	98	60	166	95	60
8	178	60	174	98	60	172	97	60	168	95	60
9	181	60	178	99	60	175	97	60	170	94	60
10	185	60	180	97	60	178	96	60	172	93	60
11	188	60	183	98	60	181	97	60	175	93	60
12	191	60	187	98	60	184	96	60	179	93	60
13	191	60	187	98	60	186	98	60	180	94	60
17	201	60	198	99	60	193	96	60	186	93	60
21	206	60	203	98	60	198	96	60	192	93	60
25	212	60	209	99	60	203	96	60	199	94	60
29	220	60	214	97	60	211	96	60	205	93	60
33	224	60	220	98	60	214	96	60	209	93	60
37	231	60	229	99	60	221	96	60	215	93	60
41	238	60	234	98	60	237	99	60[a]	224	94	60
45	246	60	240	98	60	234	95	60	228	93	60
49	258	60	254	98	60	247	96	60	239	93	60
53	268	60	265	99	60	257	96	60	247	92	59
57	282	60	277	98	60	270	96	59	259	92	59
61	289	60	284	98	59	275	95	58	262	91	59
65	299	60	293	98	59	283	95	57	269	90	58
69[b]	303	49	300	99	49	288	95	50	274	90	48
73	308	48	300	97	49	291	94	48	277	90	48
77	314	47	305	97	48	295	94	48	284	90	45
81	313	47	308	98	48	299	96	47	291	93	43
85	312	47	307	98	48	296	95	45	286	91	37
89	315	47	314	100	46	305	97	44	293	93	32
93	319	45	318	100	45	311	98	40	297	93	24
97	326	44	325	100	43	323	99	35	301	92	20
101	330	39	327	99	34	322	98	26	307	93	10
105	329	36	328	100	27	320	97	23	313	95	5
Mean for weeks											
1-13	166		162	98		161	97		157	95	
14-52	226		222	98		218	96		211	93	
53-105	308		304	99		295	96		283	92	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluation occurred during week 66.

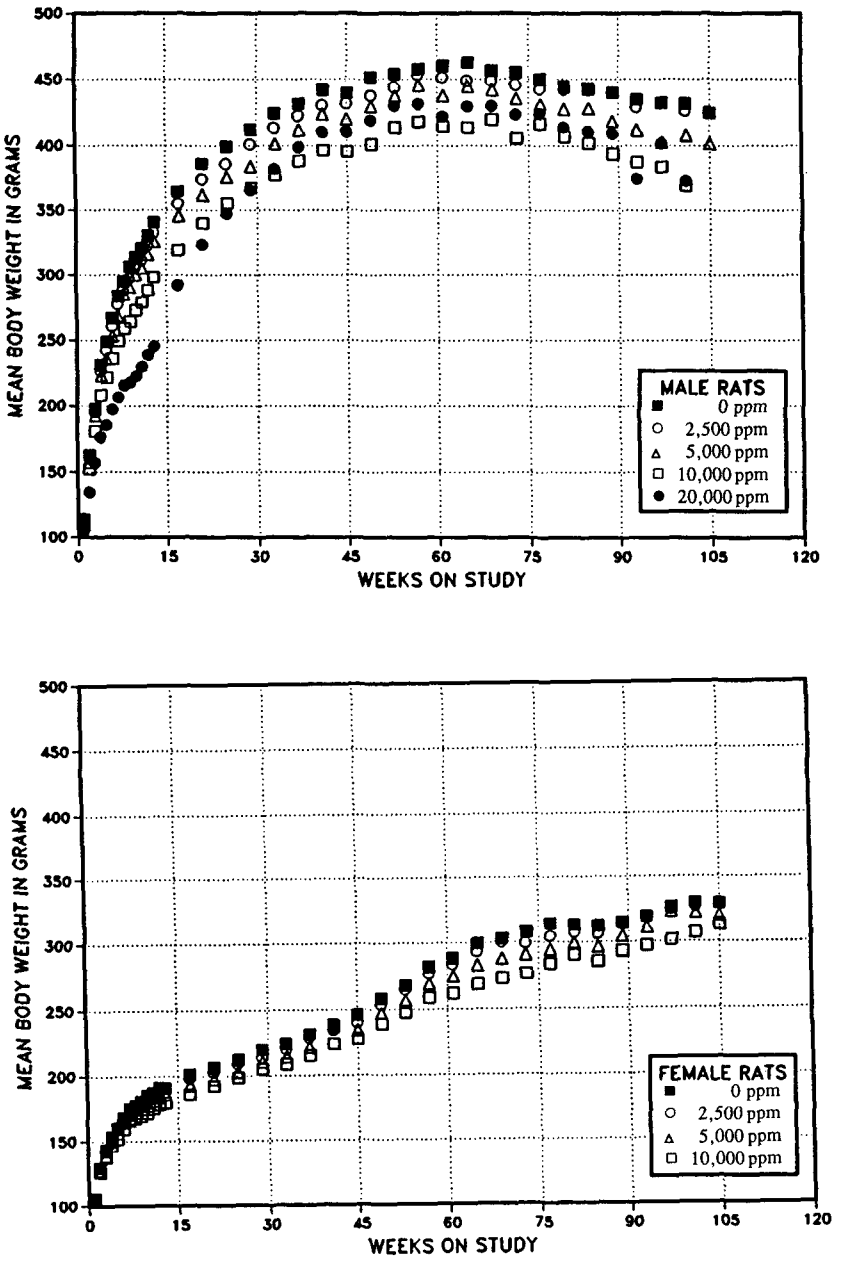


FIGURE 2
Growth Curves for Male and Female Rats Administered 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 2 Years

Pathology and Statistical Analysis

This section describes statistically significant and biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin, mammary gland, Zymbal's gland, oral cavity (pharynx, tongue, and gingiva), esophagus, forestomach, intestine (small and large), kidney, urinary bladder, lung, thyroid gland, seminal vesicle, and pancreas, and in the incidences of malignant mesothelioma and mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of 5% in at least one exposure group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Skin: The incidence of squamous cell papilloma in the 20,000 ppm stop-exposure males was significantly greater than that in the control group (Tables 7 and A3). Additionally, the incidences of keratoacanthoma, and of squamous and basal cell neoplasms (combined) in 5,000 and 10,000 ppm continuous-exposure males and in the 20,000 ppm stop-exposure males were significantly greater than that in the control group (Tables 7 and A3). The incidences of keratoacanthoma, and of squamous and basal cell neoplasms (combined) in 5,000 and 10,000 ppm continuous-exposure males and in the 20,000 ppm stop-exposure males exceeded NTP historical control range (Tables 7 and A4a). These masses were all observed at necropsy and occurred at various sites on the body (tail, leg, neck, etc.). Eight of the squamous cell papillomas in exposed male rats occurred on the lips; the one papilloma that occurred in the control group was observed on the tail. Papillomas were exophytic masses of well-differentiated squamous epithelium. Keratoacanthomas extended slightly above the skin surface but generally formed plaque-like masses within the skin and consisted of well-differentiated squamous epithelium with abundant keratin formation. One 20,000 ppm stop-exposure male had squamous cell carcinoma.

The incidences of basal cell and sebaceous gland neoplasms (trichoepithelioma, basal cell adenoma, sebaceous gland adenoma, or basal cell carcinoma [combined]) in 10,000 ppm continuous-exposure males and 20,000 ppm stop-exposure males were greater than that in the control group (Tables 7 and A3). Most of these neoplasms were benign neoplasms and ranged from well-differentiated sebaceous gland adenoma to basal cell adenoma that had morphologic patterns consisting of cords or nests of basal cells as well as areas with sebaceous or squamous differentiation or development of hair follicles (trichoepithelioma).

In addition to epithelial neoplasms of the skin, there were significantly increased incidences of subcutaneous skin neoplasms in all continuous-exposure groups of males (Tables 7 and A3). These subcutaneous masses were located along the lateral and ventral abdominal wall and were also present in the axillary and inguinal areas. Often these large masses were the primary reason for the moribund sacrifice of these rats. In the 5,000 and 10,000 ppm groups of males, there were multiple fibromas in four and six rats, respectively; multiple sarcomas were present in one male in the 10,000 ppm group (Table A1). The incidences of fibroma, fibrosarcoma, or sarcoma (combined) in 2,500, 5,000 and 10,000 ppm continuous-exposure males and in the 20,000 ppm stop-exposure males exceeded the NTP historical control range (Tables 7 and A4b). Fibroma consisted of a uniform mass of spindle-shaped cells within a dense matrix of collagen fibers (Plate 1). Except for the absence of a glandular component, fibromas were morphologically similar to fibroadenomas observed in the same exposure groups of male rats. Sarcomas were composed of anaplastic, spindle-shaped cells that had indistinct and variable growth patterns. Because of the absence of sufficient differentiation of the sarcomas, it was not possible to determine the cell of origin for these malignant mesenchymal tumors.

TABLE 7
Incidences of Skin Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
15-Month Interim Evaluation					
Skin[b]	9	7	9	5	—[d]
Squamous Cell Papilloma[c]	0	1	0	1	
2-Year Study					
Skin	51	53	51	55	59
Squamous Cell Papilloma	1	0	2	5	11**
Keratoacanthoma	3	5	11*	16**	10**
Squamous Cell Carcinoma	0	0	0	0	1
Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma	4	5	13*	20**	19**
Trichoepithelioma	0	0	0	1	1
Sebaceous Gland Adenoma	0	1	0	2	2
Basal Cell Adenoma	0	1	0	3**	6**
Basal Cell Carcinoma	0	0	2	2	0
Trichoepithelioma, Sebaceous Gland Adenoma, Basal Cell Adenoma, or Basal Cell Carcinoma	0	2	2	7**	9**
Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma or Carcinoma, or Squamous Cell Carcinoma[e]	4	6	14**	24**	21**
Subcutaneous Tissue	51	53	51	55	59
Fibroma	2	8*	11**	15**	7**
Fibrosarcoma	0	1	0	0	1
Sarcoma	0	0	2	3**	2
Fibroma, Fibrosarcoma, or Sarcoma[f]	2	9*	13**	16**	10**

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test or the life table test (subcutaneous neoplasms).
** $P \leq 0.01$
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with skin examined microscopically
[c] Number of animals with neoplasms
[d] No animals from the stop-exposure group were examined at the 15-month interim evaluation
[e] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 101/1,353 (7.5% ± 3.1%); range 2%-16%
[f] Historical incidence: 89/1,353 (6.6% ± 4.3%); range 0%-16% (includes data for neurofibrosarcoma, fibrosarcoma, sarcoma, neurofibroma, and fibroma)

Mammary Gland: The incidences of benign mammary gland neoplasms (fibroadenoma and fibroadenoma or adenoma [combined]) were significantly greater in the stop-exposure group of male rats and in all continuous-exposure groups of male rats than in the control group (Tables 8 and A3). In female rats, the incidences of fibroadenoma and of fibroadenoma, adenoma, or carcinoma (combined) in all exposed groups were greater than those in the control group (Tables 8 and B3). In male rats, the incidences of fibroadenoma or adenoma (combined) in the 5,000 and 10,000 ppm groups exceeded the NTP historical control range (Tables 8 and A4c). In female rats, the incidence of fibroadenoma, adenoma, or carcinoma (combined) in all exposure groups exceeded the historical control range (Tables 8 and B4a). The incidences of multiple fibroadenoma in all exposed female groups were greater than that in the control group (Table B1). Fibroadenomas were morphologically similar in exposed and control groups and consisted of multiple foci of a well-differentiated epithelial component, forming ductules and alveoli that were surrounded by a dense proliferation of fibrous connective tissue. While the connective tissue component was prominent and sometimes composed the major portion of the fibroadenoma, the adenomas consisted predominantly of glands, ductules, or alveoli with little or no apparent fibrous stroma. Incidences of carcinoma in exposed groups did not differ significantly from those in the control groups (Tables 8, A3, and B3).

TABLE 8
Incidences of Mammary Gland Neoplasms in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
Mammary Gland					
Fibroadenoma					
Overall rate[b]	0/51 (0%)	4/53 (8%)	6/51 (12%)	6/55 (11%)	5/60 (8%)
Adjusted rate[c]	0.0%	18.9%	42.6%	51.6%	57.6%
Terminal rate[d]	0/26 (0%)	3/20 (15%)	5/13 (38%)	0/1 (0%)	0/0
First incidence (days)	—[f]	725	726	576	592
Logistic regression test[e]	P<0.001	P=0.034	P<0.001	P=0.003	P=0.001
Fibroadenoma, Multiple					
Overall rate	0/51 (0%)	1/53 (2%)	2/51 (4%)	0/55 (0%)	1/60 (2%)
Adenoma					
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	1/55 (2%)	0/60 (0%)
Fibroadenoma or Adenoma[g]					
Overall rate	0/51 (0%)	4/53 (8%)	7/51 (14%)	7/55 (13%)	5/60 (8%)
Adjusted rate	0.0%	18.9%	44.8%	53.2%	57.6%
Terminal rate	0/26 (0%)	3/20 (15%)	5/13 (38%)	0/1 (0%)	0/0
First incidence (days)	—	725	684	576	592
Logistic regression test	P<0.001	P=0.034	P<0.001	P=0.002	P=0.001

(continued)

TABLE 8
Incidences of Mammary Gland Neoplasms in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female				
15-Month Interim				
Mammary Gland	10	9	7	8
Fibroadenoma	1	1	0	3
2-Year Study				
Mammary Gland				
Fibroadenoma				
Overall rate	25/50 (50%)	45/51 (88%)	46/53 (87%)	45/52 (87%)
Adjusted rate	60.7%	95.7%	97.9%	100.0%
Terminal rate	20/36 (56%)	25/27 (93%)	22/23 (96%)	5/5 (100%)
First incidence (days)	516	460	565	460
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Fibroadenoma, Multiple				
Overall rate	6/50 (12%)	37/51** (73%)	40/53** (75%)	37/52** (71%)
Adenoma				
Overall rate	0/50 (0%)	2/51 (4%)	0/53 (0%)	0/52 (0%)
Carcinoma				
Overall rate	4/50 (8%)	4/51 (8%)	3/53 (6%)	4/52 (8%)
Adjusted rate	9.7%	12.9%	7.2%	10.6%
Terminal rate	1/36 (3%)	3/27 (11%)	0/23 (0%)	0/5 (0%)
First incidence (days)	624	404	388	432
Logistic regression test	P=0.211N	P=0.603N	P=0.341N	P=0.313N
Fibroadenoma, Adenoma, or Carcinoma[h]				
Overall rate	27/50 (54%)	47/51 (92%)	47/53 (89%)	47/52 (90%)
Adjusted rate	62.5%	97.9%	97.9%	100.0%
Terminal rate	20/36 (56%)	26/27 (96%)	22/23 (96%)	5/5 (100%)
First incidence (days)	516	404	388	432
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A negative trend or lower incidence in an exposure group is indicated by N.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 63/1,353 (4.7% ± 3.1%); range 0%-12%
[h] Historical incidence: 568/1,351 (42.0% ± 14.0%); range 8%-64%

Zymbal's Gland: The incidences of Zymbal's gland adenoma in 10,000 ppm males and of adenoma or carcinoma in 20,000 ppm stop-exposure males were significantly greater than those in the controls (Tables 9 and A3). The incidences of adenoma in all other exposed groups, and the incidences of carcinoma, or adenoma or carcinoma (combined) in all continuously exposed male and female rats were not significantly different from those of the control groups. The incidences of adenoma or carcinoma (combined) in 5,000 and 10,000 ppm continuous-exposure males, and in 20,000 ppm stop-exposure males, exceeded the NTP historical control range (Tables 9 and A4d). In the 20,000 ppm stop-exposure group, two rats developed bilateral Zymbal's gland carcinoma (Table A1). The Zymbal's gland neoplasms frequently ulcerated through the skin and in almost all instances were the primary cause of the moribund condition of the rats. These neoplasms are of modified sebaceous gland origin, and those that occurred in exposed groups were morphologically similar to the malignant Zymbal's gland neoplasms that infrequently occur in control rats. Carcinomas were expansile, invasive neoplasms that extended into the adjacent muscle and soft tissues. Two carcinomas in 10,000 ppm males, one in 20,000 ppm males, and one in a control male metastasized to the lung (Table A1).

TABLE 9
Incidences of Zymbal's Gland Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Zymbal's Gland					
Adenoma					
Overall rate[b]	0/51 (0%)	0/53 (0%)	1/51 (2%)	3/55 (5%)	2/60 (3%)
Adjusted rate[c]	0.0%	0.0%	4.3%	52.6%	7.9%
Terminal rate[d]	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—[f]	—	694	556	513
Life table test[e]	P=0.001	—	P=0.422	P=0.020	P=0.129
Carcinoma					
Overall rate	2/51 (4%)	1/53 (2%)	3/51 (6%)	2/55 (4%)	15/60 (25%)
Adjusted rate	4.1%	3.8%	7.2%	5.8%	44.7%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	334	696	592	516	222
Life table test	P=0.286	P=0.554N	P=0.467	P=0.582	P<0.001
Adenoma or Carcinoma[g]					
Overall rate	2/51 (4%)	1/53 (2%)	4/51 (8%)	5/55 (9%)	15/60 (25%)
Adjusted rate	4.1%	3.8%	11.2%	55.4%	44.7%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	334	696	592	516	222
Life table test	P=0.009	P=0.544N	P=0.286	P=0.067	P<0.001

[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with neoplasm per number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. A lower incidence in an exposure group is indicated by N.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 16/1,353 (1.2% ± 1.4%); range 0%-4%

Oral Cavity (Pharynx, Tongue, and Gingiva), Esophagus, and Forestomach: The incidences of squamous cell papilloma of the oral cavity in exposed males (continuous- and stop-exposure) were significantly greater than that in the control group (Tables 10 and A3). Additionally, the incidences of squamous cell papilloma of the esophagus in male and female rats exposed to 10,000 ppm were significantly greater than those in the control groups (Tables 10, A3, and B3). These benign neoplasms were observed grossly at necropsy and consisted of well-demarcated exophytic nodular or papillary masses arising from the mucosal surface of the tongue, soft or hard palate of the pharynx, gingiva, or esophagus. In male rats these neoplasms were more commonly observed in the oral cavity (Plate 2), while in female rats the higher incidences occurred in the esophageal mucosa. Some of these esophageal squamous cell neoplasms occurred near the proximal origin of the esophagus at the posterior aspect of the pharynx. In exposed rats, the incidences of squamous cell carcinoma at these sites were not significantly different from those of the control groups; however, these malignant neoplasms occurred only in the oral cavities of exposed rats (Tables 10, A1, and B1). The incidences of squamous cell neoplasms of the oral cavity in 20,000 ppm stop-exposure males were similar to those in 10,000 ppm males (Tables 10 and A1). The incidences of squamous cell papilloma and carcinoma (combined) of the oral cavity in all exposed groups of males and 5,000 and 10,000 ppm females exceeded the NTP historical control ranges (Tables 10, A4g, and B4e).

Squamous cell papilloma of the forestomach (Plate 3) occurred in exposed groups of rats, but the incidence was only significant in 20,000 ppm stop-exposure males (Tables 10, A3, and B3). These benign squamous cell neoplasms in the forestomach were morphologically similar to those that occurred in the oral cavity and esophagus. There were no significantly increased incidences of inflammation, necrosis, or diffuse hyperplasia at these sites, but focal areas of squamous cell hyperplasia in the tongue, palate of the pharynx, or esophagus were present in a few rats from exposed groups (Tables 10, A5, and B5).

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Oral Cavity, Esophagus, and Forestomach in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
Pharynx[b]	—[d]	3	4	5	10
Palate, Epithelium, Hyperplasia, Focal[c]		1 (3.0)[e]	1 (2.0)	3 (2.0)	2 (2.0)
Tongue	—	2	5	13	9
Epithelium, Hyperplasia, Focal		0	0	4 (2.3)	3 (2.3)
Oral Cavity (Pharynx, Tongue, or Gingiva)					
Squamous Cell Papilloma					
Overall rate[f]	0/51 (0%)	4/53 (8%)	8/51 (16%)	10/55 (18%)	12/60 (20%)
Adjusted rate[g]	0.0%	20.0%	35.7%	44.2%	100.0%
Terminal rate[h]	0/26 (0%)	4/20 (20%)	3/13 (23%)	0/1 (0%)	0/0
First incidence (days)	—[j]	736 (T)	536	381	511
Logistic regression test[i]	P<0.001	P=0.033	P=0.004	P=0.005	P<0.001
Squamous Cell Carcinoma					
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	0/55 (0%)	2/60 (3%)
Squamous Cell Papilloma or Squamous Cell Carcinoma[k]					
Overall rate	0/51 (0%)	4/53 (8%)	9/51 (18%)	10/55 (18%)	13/60 (22%)
Adjusted rate	0.0%	20.0%	39.0%	44.2%	100.0%
Terminal rate	0/26 (0%)	4/20 (20%)	3/13 (23%)	0/1 (0%)	0/0
First incidence (days)	—	736 (T)	536	381	511
Logistic regression test	P<0.001	P=0.033	P=0.002	P=0.005	P<0.001
Esophagus	51	53	51	55	60
Epithelium, Hyperplasia, Focal	0	0	0	1 (2.0)	0
Squamous Cell Papilloma					
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	5/55 (9%)	0/60 (0%)
Adjusted rate	0.0%	0.0%	3.2%	62.6%	0.0%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—	—	662	549	—
Logistic regression test	P=0.001	—	P=0.507	P=0.021	—
Squamous Cell Carcinoma					
Overall rate	0/51 (0%)	0/53 (0%)	0/51 (0%)	1/55 (2%)	0/60 (0%)
Forestomach	51	53	51	55	59
Mucosa, Hyperplasia	4 (1.8)	12 (1.8)	6 (2.3)	6 (2.0)	6 (1.5)
Squamous Cell Papilloma[l]					
Overall rate	0/51 (0%)	0/53 (0%)	0/51 (0%)	1/55 (2%)	5/60 (8%)
Adjusted rate	0.0%	0.0%	0.0%	3.8%	26.7%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—	—	—	604	511
Logistic regression test	P<0.001	—	—	P=0.571	P=0.028

(continued)

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Oral Cavity, Esophagus, and Forestomach in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female				
Pharynx	1	1	1	2
Palate, Epithelium, Hyperplasia, Focal	0	0	0	1 (1.0)
Tongue	1	3	6	6
Epithelium, Hyperplasia, Focal	0	1 (2.0)	1 (2.0)	1 (2.0)
Oral Cavity (Pharynx or Tongue)				
Squamous Cell Papilloma				
Overall rate	2/50 (4%)	2/51 (4%)	4/53 (8%)	5/52 (10%)
Adjusted rate	5.6%	7.4%	11.5%	47.0%
Terminal rate	2/36 (6%)	2/27 (7%)	1/23 (4%)	2/5 (40%)
First incidence (days)	738 (T)	738 (T)	627	577
Logistic regression test	P=0.054	P=0.588	P=0.348	P=0.094
Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	1/51 (2%)	1/53 (2%)	1/52 (2%)
Adjusted rate	0.0%	3.2%	2.6%	3.6%
Terminal rate	0/36 (0%)	0/27 (0%)	0/23 (0%)	0/5 (0%)
First incidence (days)	—	723	662	631
Logistic regression test	P=0.408	P=0.494	P=0.544	P=0.591
Squamous Cell Papilloma or Squamous Cell Carcinoma[m]				
Overall rate	2/50 (4%)	3/51 (6%)	5/53 (9%)	6/52 (12%)
Adjusted rate	5.6%	10.4%	13.8%	48.9%
Terminal rate	2/36 (6%)	2/27 (7%)	1/23 (4%)	2/5 (40%)
First incidence (days)	738 (T)	723	627	577
Logistic regression test	P=0.042	P=0.424	P=0.236	P=0.064
Esophagus	50	51	53	52
Epithelium, Hyperplasia, Focal	0	0	0	1 (2.0)
Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/51 (0%)	1/53 (2%)	10/52 (19%)
Adjusted rate	0.0%	0.0%	4.3%	42.4%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	0/5 (0%)
First incidence (days)	—	—	738 (T)	474
Logistic regression test	P<0.001	—	P=0.411	P=0.002

(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with organ examined microscopically
[c] Number of animals with lesion
[d] Organ not examined at this exposure level
[e] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[f] Number of animals with neoplasm per number of animals necropsied
[g] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[h] Observed incidence in animals surviving until the end of the study
[i] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[j] Not applicable; no neoplasms in animal group
[k] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 11/1,353 (0.8% ± 1.4%); range 0%-4% (includes data for oral mucosa, tongue, pharynx, tooth, and lip)
[l] Historical incidence: 3/1351 (0.2% ± 0.6%); range 0%-2%
[m] Historical incidence: 12/1,351 (0.9% ± 1.4%); range 0%-6% (includes data for oral mucosa, tongue, pharynx, tooth, and lip)

Small and Large Intestine: The incidence of adenoma or carcinoma (combined) of the small intestine in 20,000 ppm stop-exposure males was greater than that in the control group (Tables 11 and A1), although the difference was not statistically significant, and the incidence exceeded the NTP historical control range (Tables 11 and A4j). The carcinomas were characterized by extensive invasion of the muscular wall of the intestine and a marked scirrhous response around and within the neoplasm. Several carcinomas contained cystic areas, and one carcinoma contained an area of osseous metaplasia (Table A5). One male from the stop-exposure group exhibited focal hyperplasia with osseous metaplasia in the mucosa of the small intestine (Table A5).

In the large intestine of males, there was a significant positive trend in the incidences of adenoma (adenomatous polyp) (Tables 11 and A3). In 20,000 ppm stop-exposure males, the incidence of adenoma of the large intestine was significantly greater than that in the control group. Additionally, the incidences of adenoma or carcinoma (combined) in the large intestine of 20,000 ppm male rats were significantly greater than that in the control group and exceeded the NTP historical control range (Tables 11, A3, and A4i). Adenomas of the large intestine were all generally similar polypoid masses extending into the intestinal lumen and composed of irregularly shaped, distended glands lined by a tall columnar epithelium (Plate 4).

In females, one rat in the 5,000 ppm group had a carcinoma in the small intestine, and one rat in the 2,500 ppm group had an adenoma of the large intestine (Table B1).

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Intestine in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Small Intestine[b]	51	53	51	53	59
Mucosa, Hyperplasia[c]	0	0	0	1 (4.0)[d]	0
Mucosa, Hyperplasia, Cystic	0	0	0	0	1 (3.0)
Adenoma	0	0	0	0	1
Carcinoma	0	0	0	2	4
Adenoma or Carcinoma[e]	0	0	0	2	5*
Large Intestine	51	53	51	55	59
Adenoma	0	0	3	4	10*
Carcinoma	0	0	0	0	2
Adenoma or Carcinoma[f]	0	0	3	4	11**

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with organ examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 7/1,353 (0.5% ± 1.1%); range 0%-4% (includes data for duodenum, ileum, and jejunum)
[f] Historical incidence: 1/1,353 (0.1% ± 0.4%); range 0%-2% (includes data for cecum, colon, and rectum)

Mesothelium: In males in the 5,000 and 10,000 ppm continuous-exposure groups and in the 20,000 ppm stop-exposure group, the incidences of mesothelioma were significantly greater than that in the control group (Tables 12 and A3). In each of these groups the incidence of mesothelioma exceeded the NTP historical control range (0%-8%; Table A4k). In some rats, the more widespread mesotheliomas were considered to be the cause of death. Mesotheliomas typically covered portions or most of the testis and epididymis. Some of these neoplasms extended throughout the abdominal cavity and formed masses on the serosal surfaces of the mesentery, pancreas, intestine, or spleen. Typically, mesothelioma consisted of cuboidal cells that formed papillary and tubular structures as well as multilayered plaques on the testes and abdominal viscera (Plate 5). Invasion into the tissues of abdominal viscera and metastatic lesions in the thoracic lymph nodes was a feature of the more highly malignant mesotheliomas.

TABLE 12
Incidences of Malignant Mesothelioma in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
15-Month Interim Evaluation					
All Organs					
Malignant Mesothelioma					
Overall rate[b]	0/9 (0%)	1/7 (14%)	1/9 (11%)	0/5 (0%)	—[c]
2-Year Study					
All Organs					
Malignant Mesothelioma[d]					
Overall rate	0/51 (0%)	3/53 (6%)	8/51 (16%)	9/55 (16%)	26/60 (43%)
Adjusted rate[e]	0.0%	7.7%	43.3%	100.0%	91.5%
Terminal rate[f]	0/26 (0%)	0/20 (0%)	4/13 (31%)	1/1 (100%)	0/0
First incidence (days)	—[h]	586	681	495	365
Logistic regression test[g]	P<0.001	P=0.157	P<0.001	P=0.003	P<0.001

[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with neoplasm per number of animals necropsied
[c] No animals from the stop-exposure group were examined at the 15-month interim evaluation.
[d] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 40/1,353 (3.0% ± 2.4%); range 0%-8%
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Not applicable; no neoplasms in animal group

Kidney and Urinary Bladder: In male rats, the incidence of renal tubule adenoma in the 10,000 ppm group was marginally but significantly greater than that in the control group; a single adenoma also occurred in one male in the 5,000 ppm group and in one male in the 20,000 ppm stop-exposure group (Tables 13, A1, and A3). However, the incidences of renal tubule adenoma in all exposed groups were within the NTP historical control range (Tables 13 and A4l). The incidences of renal tubule hyperplasia in the exposed groups were similar to the incidence in the control group (Tables 13 and A5). In female rats, renal tubule adenoma occurred in one animal in the 2,500 ppm group. Although renal tubule adenoma is rare in female rats, this single incidence was within the NTP historical control range (Tables 13 and B4i).

In the urinary bladder, a transitional cell papilloma was observed in one 10,000 ppm male at the 15-month interim evaluation (Tables 14 and A1). Transitional cell papillomas were also observed in males from the 5,000 and 10,000 ppm groups and the 20,000 ppm stop-exposure group at 2 years; one 10,000 ppm male and one 20,000 ppm stop-exposure male had transitional cell carcinomas (Table A1). In the current NTP historical database there are no occurrences of transitional cell carcinoma of the urinary bladder; three papillomas have occurred in 1,329 male rats.

Incidences and types of treatment-related non-neoplastic lesions in the kidney and urinary bladder at 15 months and 2 years were similar to those observed at the same sites in the 13-week studies. In the 2-year study, these lesions generally occurred earlier in males than in females, and the incidences and severities in males were greater than those in females. By 15 months and after 2 years, in addition to papillary degeneration, there were increases in the incidences of hyperplasia of the renal papilla epithelium, hyperplasia of the transitional epithelium lining of the renal pelvis, and focal renal tubule atrophy in male rats (Tables 13 and A5). Necrosis, mineralization, and hemorrhage were components of the more severe examples of papillary degeneration that occurred in the 2-year study (Plate 6), but not in the 13-week studies. There were also treatment-related cortical lesions consisting of focal linear or wedge-shaped areas of atrophy or collapse of renal tubules with fibrosis and inflammation. Hyperplasia of the epithelium lining the papilla and pelvis was not always associated with the degree of severity of the papillary degeneration. The incidence and severity of nephropathy were similar in exposed and control groups of male and female rats, although the average severity was slightly decreased in exposed males (Tables 13 and A5). In the urinary bladder of male rats, transitional cell hyperplasia was present, primarily in the 20,000 ppm stop-exposure group (Tables 14 and A5).

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
15-Month Interim Evaluation					
Kidney[b]	9	7	9	5	—[d]
Atrophy, Focal[c]	0	0	0	1 (3.0)[e]	
Papillary Degeneration	0	0	2 (2.5)	4** (1.5)	
Papillary Epithelial Hyperplasia	1 (1.0)	0	1 (2.0)	5** (2.0)	
Transitional Cell Carcinoma	0	0	0	1	
2-Year Study					
Kidney	51	53	51	55	59
Atrophy, Focal	0	0	0	5* (3.0)	0
Papillary Degeneration	0	5 (1.4)	30** (1.5)	29** (2.1)	16** (1.2)
Papillary Epithelial Hyperplasia	10 (1.0)	20** (1.3)	25** (1.3)	47** (1.9)	21* (1.1)
Pelvis, Transitional Epithelium, Hyperplasia	0	0	0	4	4
Nephropathy	51 (2.2)	53 (2.2)	51 (1.8)	53 (1.7)	58 (1.6)
Renal Tubule, Epithelium, Hyperplasia, Focal	0	0	2	0	0
Renal Tubule Adenoma[f]	0	0	1	3**	1
Transitional Cell Carcinoma	0	0	0	0	1
Female					
2-Year Study					
Kidney	50	51	53	52	
Atrophy, Focal	0	2 (1.5)	1 (2.0)	7* (2.9)	
Papillary Degeneration	0	1 (1.0)	3 (1.7)	17** (2.1)	
Papillary Epithelial Hyperplasia	0	1 (1.0)	1 (1.0)	7** (1.4)	
Pelvis, Transitional Epithelium, Hyperplasia	0	1	0	0	
Nephropathy	48 (1.4)	50 (1.2)	50 (1.3)	50 (1.3)	
Renal Tubule Adenoma[g]	0	1	0	0	

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test (interim evaluation) or the logistic regression test (2-year study)
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with kidney examined microscopically
[c] Number of animals with lesion
[d] No animals from the stop-exposure group were examined at the 15-month interim evaluation.
[e] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[f] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 9/1,350 (0.7% ± 1.5%); range 0%-6%
[g] Historical incidence: 1/1,348 (0.1% ± 0.4%); range 0%-2%

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Urinary Bladder in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
15-Month Interim Evaluation					
Urinary Bladder[b]	9	7	9	5	
Transitional Cell Papilloma[c]	0	0	0	1	—[d]
2-Year Study					
Urinary Bladder	51	53	51	55	59
Transitional Cell Hyperplasia	0	0	1 (1.0)[e]	3 (1.3)	10 (1.1)
Transitional Cell Papilloma	0	0	1	2	1
Transitional Cell Carcinoma	0	0	0	1	1
Transitional Cell Papilloma or Carcinoma[f]	0	0	1	3	2
Female					
2-Year Study					
Urinary Bladder	50	51	53	52	
Transitional Cell Hyperplasia	0	0	1 (2.0)	0	
Transitional Cell Papilloma	0	1	0	0	

[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with urinary bladder examined microscopically
[c] Number of animals with lesion
[d] No animals in the stop-exposure group were examined at the 15-month interim evaluation.
[e] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[f] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 3/1,329 (0.23% ± 0.64%); range 0%-2%

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 10,000 ppm continuous-exposure males and 20,000 ppm stop-exposure males were significantly greater than that in the control group (Tables 15 and A3) and approached or exceeded the upper limit of the NTP historical control range (Tables 15 and A4m). Multiple carcinomas were present in one 10,000 ppm male and one 20,000 ppm stop-exposure male (Table A1). The adenomas consisted of papillary and solid areas of well-differentiated, cuboidal to columnar epithelium. Carcinomas had increased cellular and nuclear atypia with local invasion and areas of mesenchymal cell proliferation or fibrosis. Metastatic neoplasms were not present. Squamous cell carcinoma was present in the lung of three male rats from the 20,000 ppm stop-exposure group (Table 15). This neoplasm is very rare in control rats, and none appear in the NTP historical database of 1,350 control male rats from dosed feed studies. Squamous cell carcinoma of the lung is morphologically similar to malignant squamous cell neoplasms that occur at other sites. In this study, these were locally invasive neoplasms composed of squamous cells, abundant keratin production, and local scirrhous response. One squamous cell carcinoma was metastatic to the brain, heart, adrenal gland, pancreas, and other abdominal viscera. In male rats there was also a significant increase in the incidence of alveolar/bronchiolar hyperplasia in the 20,000 ppm stop-exposure group. In female rats, a few alveolar/bronchiolar neoplasms occurred only in exposed groups (0/50, 1/51, 0/53, 2/52; Table B1) but the incidences were not significantly different from those in the control group and were within the NTP historical control range (0%-10%; Table B4j).

TABLE 15
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Lung[b]	51	53	51	55	60
Alveolar/bronchiolar Hyperplasia[c]	3 (2.3)[d]	4 (1.8)	5 (1.4)	7 (1.7)	14** (1.6)
Alveolar/bronchiolar Adenoma					
Overall rate[e]	1/51 (2%)	0/53 (0%)	3/51 (6%)	1/55 (2%)	4/60 (7%)
Adjusted rate[f]	2.9%	0.0%	18.6%	10.0%	100.0%
Terminal rate[g]	0/26 (0%)	0/20 (0%)	2/13 (15%)	0/1 (0%)	0/0
First incidence (days)	696	—[i]	684	682	513
Logistic regression test[h]	P=0.182	P=0.515N	P=0.211	P=0.644	P=0.086
Alveolar/bronchiolar Carcinoma					
Overall rate	0/51 (0%)	1/53 (2%)	0/51 (0%)	3/55 (5%)	3/60 (5%)
Adjusted rate	0.0%	5.0%	0.0%	59.3%	21.4%
Terminal rate	0/26 (0%)	1/20 (5%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—	736 (T)	—	620	522
Logistic regression test	P=0.005	P=0.448	—	P=0.024	P=0.118
Alveolar/bronchiolar Carcinoma, Multiple					
Overall rate	0/51 (0%)	0/53 (0%)	0/51 (0%)	1/55 (2%)	1/60 (2%)
Alveolar/bronchiolar Adenoma or Carcinoma[j]					
Overall rate	1/51 (2%)	1/53 (2%)	3/51 (6%)	4/55 (7%)	7/60 (12%)
Adjusted rate	2.9%	5.0%	18.6%	63.4%	100.0%
Terminal rate	0/26 (0%)	1/20 (5%)	2/13 (15%)	0/1 (0%)	0/0
First incidence (days)	696	736 (T)	684	620	513
Logistic regression test	P=0.003	P=0.726	P=0.211	P=0.029	P=0.011
Squamous Cell Carcinoma[k]					
Overall rate	0/51 (0%)	0/53 (0%)	0/51 (0%)	0/55 (0%)	3/60 (5%)
Adjusted rate	0.0%	0.0%	0.0%	0.0%	13.2%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—	—	—	—	365
Logistic regression test	P=0.028	—	—	—	P=0.330

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with lung examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Number of animals with neoplasm per number of animals with lung examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A lower incidence in an exposure group is indicated by N.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 44/1,350 (3.3% ± 1.9%); range 0%-8%
[k] Historical incidence: 0/1,350

Thyroid Gland: In males, the incidence of follicular cell adenoma in the 20,000 ppm stop-exposure group and the incidence of follicular cell carcinoma in the 5,000 ppm group were significantly greater than the incidences in the control group. The combined incidences of follicular cell adenoma or carcinoma in 5,000 ppm continuous-exposure males, 20,000 ppm stop-exposure males, and 10,000 ppm females were significantly greater than those in the control groups and exceeded the NTP historical control range for males and females (Tables 16, A3, A4n, B3, and B4k). In males, the highest incidence occurred in the 20,000 ppm stop-exposure group; 12 of the 20 adenomas or carcinomas that occurred in exposed rats were observed grossly. In exposed females, none of the follicular cell neoplasms were observed at necropsy. Follicular cell neoplasms in exposed rats were morphologically similar to those in control rats. Adenomas were well-demarcated masses that were generally not encapsulated and were composed of cuboidal follicular epithelium forming papillary, solid areas or an atypical follicular pattern. Follicular cell carcinomas were locally invasive neoplasms that often were associated with a scirrhous response; two of the carcinomas in exposed males metastasized to the lung or lymph nodes. Follicular cell hyperplasia was also significantly increased in male rats from the 20,000 ppm stop-exposure group (Tables 16 and A5).

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Male					
2-Year Study					
Thyroid Gland[b]	51	53	51	55	59
Follicular Cell Hyperplasia[c]	1 (3.0)[d]	0	2 (1.5)	5 (2.2)	6* (1.8)
Follicular Cell Adenoma					
Overall rate[e]	0/51 (0%)	1/53 (2%)	2/51 (4%)	2/55 (4%)	7/59 (12%)
Adjusted rate[f]	0.0%	5.0%	8.4%	8.8%	39.9%
Terminal rate[g]	0/26 (0%)	1/20 (5%)	0/13 (0%)	0/1 (0%)	0/0
First incidence (days)	—[i]	736 (T)	666	608	432
Logistic regression test[h]	P=0.113	P=0.448	P=0.233	P=0.274	P=0.021
Follicular Cell Carcinoma					
Overall rate	0/51 (0%)	1/53 (2%)	4/51 (8%)	1/55 (2%)	2/59 (3%)
Adjusted rate	0.0%	2.6%	20.8%	5.9%	26.3%
Terminal rate	0/26 (0%)	0/20 (0%)	2/13 (15%)	0/1 (0%)	0/0
First incidence (days)	—	610	633	647	388
Logistic regression test	P=0.235	P=0.549	P=0.047	P=0.492	P=0.399
Follicular Cell Adenoma or Carcinoma[j]					
Overall rate	0/51 (0%)	2/53 (4%)	6/51 (12%)	3/55 (5%)	9/59 (15%)
Adjusted rate	0.0%	7.5%	27.5%	14.2%	55.7%
Terminal rate	0/26 (0%)	1/20 (5%)	2/13 (15%)	0/1 (0%)	0/0
First incidence (days)	—	610	633	608	388
Logistic regression test	P=0.055	P=0.239	P=0.013	P=0.124	P=0.009

(continued)

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Thyroid Gland in Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female				
15-Month Interim Evaluation				
Thyroid Gland				
Follicular Cell Adenoma				
Overall rate	0/10 (0%)	0/9 (0%)	0/7 (0%)	1/8 (13%)
2-Year Study				
Follicular Cell Adenoma				
Overall rate	0/50 (0%)	0/51 (0%)	2/53 (4%)	3/52 (6%)
Adjusted rate	0.0%	0.0%	6.3%	35.4%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	1/5 (20%)
First incidence (days)	—	—	508	689
Logistic regression test	P=0.021	—	P=0.320	P=0.012
Follicular Cell Carcinoma				
Overall rate	0/50 (0%)	0/51 (0%)	0/53 (0%)	1/52 (2%)
Adjusted rate	0.0%	0.0%	0.0%	20.0%
Terminal rate	0/36 (0%)	0/27 (0%)	0/23 (0%)	1/5 (20%)
First incidence (days)	—	—	—	738 (T)
Logistic regression test	P=0.032	—	—	P=0.124
Follicular Cell Adenoma or Carcinoma[k]				
Overall rate	0/50 (0%)	0/51 (0%)	2/53 (4%)	4/52 (8%)
Adjusted rate	0.0%	0.0%	6.3%	51.5%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	2/5 (40%)
First incidence (days)	—	—	508	689
Logistic regression test	P=0.003	—	P=0.320	P=0.001

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with thyroid gland examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Number of animals with neoplasm per number of animals with thyroid gland examined microscopically
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[g] Observed incidence in animals surviving until the end of the study
[h] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 23/1,343 (1.7% ± 1.6%); range 0%-6%
[k] Historical incidence: 12/1,346 (0.9% ± 1.5%); range 0%-6%

Accessory Sex Glands: There was one adenoma and one carcinoma of the seminal vesicle in male rats from the 20,000 ppm stop-exposure group (Tables 17 and A1). Neoplasms of the seminal vesicle are rare and none have occurred in rats from the current NTP historical database. The adenoma of the seminal vesicle consisted of a focally expansile mass that filled the lumen, with glandular and solid areas formed by a generally well-differentiated, closely packed, tall, columnar epithelium. The carcinoma was a highly invasive neoplasm with marked cellular atypia. Metastatic foci were present in the lung, spleen, and other abdominal viscera. At 15 months, hyperplasia of the seminal vesicle was present in a few rats from exposed groups; at 2 years the incidences of hyperplasia in males from the 10,000 ppm continuous-exposure group and the 20,000 ppm stop-exposure group were greater than the incidence in the control group (Tables 17 and A5). Hyperplasia consisted of one or more focal areas with increased cellularity of the mucosal lining of the seminal vesicle. The hyperplastic epithelium was increased in height and more closely packed compared to the cells forming normal adjacent mucosal lining; the fibrovascular stroma in the foci of hyperplasia was often more prominent than in the normal areas of the mucosa (Plate 7). Although the cellular morphology was similar to adenoma, in the focal hyperplasia, there was a lack of compression or distortion of adjacent tissue in the seminal vesicle. In the coagulating gland, which is attached to the seminal vesicle, there was a slight increase in the incidence of hyperplasia in exposed male rats. The focal areas of hyperplasia of the coagulating gland in exposed male rats were morphologically similar to those seen in the seminal vesicle.

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Seminal Vesicle in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
15-Month Interim Evaluation					
Seminal Vesicle[b]	9	7	9	5	—[d]
Hyperplasia[c]	0	2 (1.0)[e]	5* (1.2)	1 (2.0)	
2-Year Study					
Seminal Vesicle	51	53	51	55	60
Hyperplasia	1 (1.0)	6 (1.0)	4 (1.0)	16** (1.4)	33** (1.3)
Adenoma	0	0	0	0	1
Carcinoma	0	0	0	0	1
Adenoma or Carcinoma[f]	0	0	0	0	2
Coagulating gland[b]					
Hyperplasia	0	1 (1.0)	0	2 (1.0)	3 (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with lesion per number of animals necropsied
[c] Number of animals with lesion
[d] No animals in the stop-exposure group were examined at the 15-month interim.
[e] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[f] Historical incidence for 2-year NTP feed studies with untreated control groups: 0/1,353

Hematopoietic System: The incidences of mononuclear cell leukemia in male rats from the 5,000 and 10,000 ppm continuous-exposure groups and the 20,000 ppm stop-exposure group were significantly greater than that in the control group (Tables 18 and A3). The incidence of mononuclear cell leukemia in the 5,000 ppm group of males exceeded the NTP historical control range (Tables 18 and A4o). Infiltration of leukemic cells generally involved numerous organs and this neoplasm was frequently considered to be the cause of death for exposed and control rats. The incidences of fibrosis of the spleen were slightly increased in 5,000 and 10,000 ppm males, and the 20,000 ppm stop-exposure males (Tables 18 and A5). This lesion is often present in the spleen of rats with mononuclear cell leukemia which was also increased in these three groups. Lymphoid hyperplasia of the mandibular lymph node in 20,000 ppm stop-exposure males and hematopoiesis of the spleen in 10,000 ppm males and females and 20,000 ppm stop-exposure males, were also considered secondary changes that were slightly increased over the background incidence typically seen in control rats (Tables 18, A5, and B5). In male rats the increased incidence of lymphoid hyperplasia was seen primarily in the regional mandibular lymph node of rats with Zymbal's gland carcinoma. Splenic hematopoiesis was often present in rats with multiple neoplasms, including carcinoma of the Zymbal's, mammary, or clitoral gland.

TABLE 18
Incidences of Mononuclear Cell Leukemia and Nonneoplastic Lesions in the Hematopoietic System in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
2-Year Study					
Lymph node, mandibular[b]	49	52	49	55	59
Hyperplasia[c]	4 (2.3)[d]	2 (2.0)	2 (3.5)	3 (2.7)	10** (2.8)
Spleen	51	53	51	54	60
Fibrosis, focal	15 (2.0)	10 (2.1)	22* (2.2)	24** (2.3)	28** (2.4)
Hematopoiesis	1 (3.0)	3 (3.0)	3 (2.7)	8* (2.8)	17** (2.9)
Mononuclear Cell Leukemia[e]					
Overall rate[f]	27/51 (53%)	29/53 (55%)	40/51** (78%)	34/55** (62%)	25/60** (42%)

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test.
** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test or the life table test (mononuclear cell leukemia).
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with organ examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 661/1,353 (48.9% ± 8.8%); range 32%-62%
[f] Number of animals with neoplasm per number of animals necropsied

Pancreas: The incidences of pancreatic acinar adenoma in all groups of exposed males were slightly greater than the incidence in controls, and the increase was significant in the 5,000 ppm group (Tables 19 and A3). The incidence in each group of exposed males was within the historical control range (0%-10%; Tables 19 and A4p). Acinar adenomas were discrete, nodular masses that slightly compressed or displaced surrounding pancreatic tissue. Adenomas were composed of glands or irregularly formed acini of generally well-differentiated pancreatic acinar cells, some of which varied slightly in size and shape compared to normal acinar cells.

The incidences of hyperplasia in all exposed groups of male rats were significantly greater than the incidence in the control group (Tables 19 and A5). These minimal to mild focal lesions were morphologically similar to the adenomas but were smaller and did not compress or distort surrounding tissue. There was minimal alteration of the acinar structure and minimal variation in cell size compared to the normal acinar cells.

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Pancreas in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm[a] (Stop-Exposure)
Pancreas, Acinar Cell[b]	51	53	51	53	59
Focal Hyperplasia[c]	3 (1.7)[d]	9* (1.9)	12* (1.3)	14** (1.8)	27** (2.0)
Acinar Cell Adenoma[e]					
Overall rate[f]	1/51 (2%)	2/53 (4%)	4/51 (8%)	3/53 (6%)	3/59 (5%)
Adjusted rate[g]	3.8%	10.0%	30.8%	34.1%	8.5%
Terminal rate[h]	1/26 (4%)	2/20 (10%)	4/13 (31%)	0/1 (0%)	0/0
First incidence (days)	736 (T)	736 (T)	736 (T)	604	507
Logistic regression test[i]	P=0.005	P=0.408	P=0.033	P=0.089	P=0.447

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Ten male rats receiving 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed were evaluated at 3 months. The remaining 60 male rats in this group received control feed until the end of the 2-year study.
[b] Number of animals with pancreas examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[e] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 24/1,340 (1.8% ± 2.3%); range 0%-10%
[f] Number of animals with neoplasm per number of animals with pancreas examined microscopically
[g] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality.
[h] Observed incidence in animals surviving until the end of the study
[i] In the control column are the P values associated with the trend test (the 20,000 ppm stop-exposure group was excluded from the trend test). In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.

MICE

13-WEEK STUDY

Five male and four female mice, dispersed among control and exposed groups, died during the study (Table 20). The final mean body weights and body weight gains of 1,250, 2,500, 5,000, and 10,000 ppm males and females and of 625 ppm females were significantly lower than those of the controls. Feed consumption by exposed mice was generally higher than that by controls throughout the study (Table 20). Dietary levels of 625, 1,250, 2,500, 5,000, and 10,000 ppm delivered average daily doses of 100, 200, 500, 1,300, and 3,000 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight to males and 140, 300, 600, 1,200, and 2,900 mg/kg to females. Clinical findings included abnormal posture and hypoactivity in 10,000 ppm male and female mice.

At the end of the study, serum blood urea nitrogen concentrations were increased in 5,000 ppm females and 10,000 ppm males and females (Table G2). Additionally, decreased urine specific gravity occurred in 10,000 ppm females. Renal papillary necrosis with tubular regeneration and fibrosis occurred in males exposed to 2,500 ppm or greater and in females exposed to 10,000 ppm. This would be consistent with the blood urea nitrogen concentration increases (azotemia) and the isosthenuric specific gravity.

The absolute and relative weights of several organs in 5,000 and 10,000 ppm animals were lower than those in the control group (Table F4). These findings were attributed to the low body weights in these groups.

In males exposed to 5,000 or 10,000 ppm, weights of the right cauda and right epididymis were significantly lower than those of control males and decreased with increasing exposure level (Table H2). In females, estrous cycle length increased with increasing exposure level, but the differences from the controls were not statistically significant.

TABLE 20
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	22.7 ± 0.4	33.3 ± 0.8	10.6 ± 0.7		4.1	4.6
625	8/10[d]	22.3 ± 0.3	31.7 ± 0.9	9.5 ± 0.6	95	4.4	4.5
1,250	10/10	22.7 ± 0.4	30.9 ± 0.8*	8.2 ± 0.6**	93	4.3	4.4
2,500	10/10	22.8 ± 0.3	29.4 ± 0.4**	6.6 ± 0.3**	88	5.0	5.0
5,000	10/10	22.2 ± 0.3	26.1 ± 0.3**	3.9 ± 0.4**	78	5.7	6.7
10,000	7/10[e]	22.7 ± 0.4	21.7 ± 0.5**	−0.8 ± 0.6**	65	5.5	7.5
Female							
0	9/10[f]	17.9 ± 0.3	30.2 ± 0.9	12.3 ± 0.8		4.9	4.6
625	9/10[g]	17.6 ± 0.3	28.4 ± 0.8*	10.7 ± 0.6*	94	4.8	5.6
1,250	9/10[g]	18.0 ± 0.3	27.8 ± 0.8**	9.7 ± 0.7**	92	5.3	5.7
2,500	9/10[h]	17.6 ± 0.2	25.5 ± 0.2**	7.9 ± 0.2**	85	5.3	5.7
5,000	9/10[i]	17.5 ± 0.3	22.3 ± 0.3**	4.9 ± 0.3**	74	5.0	4.4
10,000	10/10	17.8 ± 0.3	17.9 ± 0.4**	0.1 ± 0.4**	59	5.0	5.4

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Week of death: 9, 9
[e] Week of death: 2, 2, 3
[f] Week of death: 6
[g] Week of death: 8
[h] Week of death: 2
[i] Week of death: 7

There were no treatment-related gross lesions in exposed mice from the 13-week study. Treatment-related microscopic lesions were present in the kidney and urinary bladder of male and female mice (Table 21). In the kidney, there was an exposure- and treatment-related increase in the incidence of papillary necrosis. In the cortex of the kidney, there were foci of renal tubule regeneration and fibrosis. These lesions were present in 2,500, 5,000, and 10,000 ppm male mice and in the 10,000 ppm females. Papillary necrosis involved both the interstitial and renal tubule epithelium at the tip of the renal papilla. Renal tubule regeneration consisted of multiple, focal lesions in the cortex characterized by degeneration and regeneration of tubule epithelium; minimal to mild fibrosis was frequently present in the areas of regeneration. In the urinary bladder of mice from the 5,000 and 10,000 ppm groups there was mild hyperplasia of the transitional epithelium. In seven of nine female mice from the 10,000 ppm group, there was also a minimal inflammatory cell infiltration in the urinary bladder mucosa and focal necrosis of the transitional cell epithelium.

TABLE 21
Incidences of Selected Nonneoplastic Lesions in Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
Kidney[a]	10	10	10	10	10	10
Necrosis, Papillary[b]	0	0	0	5* (1.2)[c]	4* (1.5)	9** (2.2)
Regeneration, Renal Tubule	0	0	0	4* (1.3)	4* (1.5)	7** (2.3)
Fibrosis	0	0	0	4* (1.3)	2 (1.5)	7** (2.1)
Urinary Bladder	10	10	10	10	10	8
Hyperplasia	0	0	0	0	4* (1.0)	7** (2.0)
Female						
Kidney	10	10	10	10	10	10
Necrosis, Papillary	0	0	0	0	0	2 (1.0)
Regeneration, Renal Tubule	0	0	0	0	0	4* (1.8)
Fibrosis	0	0	0	0	0	2 (1.5)
Urinary Bladder	10	10	10	10	10	10
Hyperplasia	0	0	0	0	10** (2.0)	9** (1.6)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Dose Selection Rationale: Based on lower final mean body weights and organ weights in 5,000 and 10,000 ppm males and females, and the presence of kidney (papillary necrosis) and urinary bladder lesions in the 2,500, 5,000, and 10,000 ppm males and females in the 13-week feed study, the high dose selected for the 2-year feed study in male and female mice was 1,250 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 22 and in the Kaplan-Meier survival curves in Figure 3. Survival of 1,250 ppm males and females was significantly lower than that of the respective controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed male and female mice were similar to controls throughout the study (Figure 4 and Tables 23 and 24). Final mean body weights were also generally similar to those of controls. Feed consumption by exposed male and female mice was similar to that by controls (Tables J3 and J4). Dietary levels of 312, 625, and 1,250 ppm delivered average daily doses of 35, 70, and 140 mg 2,2-bis(bromomethyl)-1,3-propanediol/kg body weight to males and 40, 80, and 170 mg/kg to females. Clinical findings included swelling, discharge, and tissue masses involving the eye in exposed mice.

TABLE 22
Survival of Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	9	10	10
Accidental deaths[a]	0	0	0	1
Missing[a]	0	0	0	1
Moribund	3	12	11	13
Natural deaths	5	3	4	5
Animals surviving to study termination	42	36	35	30
Percent probability of survival at the end of study[b]	84	71	70	63
Mean survival (days)[c]	710	675	698	684
Survival analysis[d]	P=0.054	P=0.169	P=0.174	P=0.038
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	8	10	9	10
Moribund	9	14	14	29
Natural deaths	6	6	11	10
Animals surviving to study termination	37	30	26	11
Percent probability of survival at the end of study	71	60	51	22
Mean survival (days)	690	685	691	625
Survival analysis	P<0.001	P=0.422	P=0.117	P<0.001

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

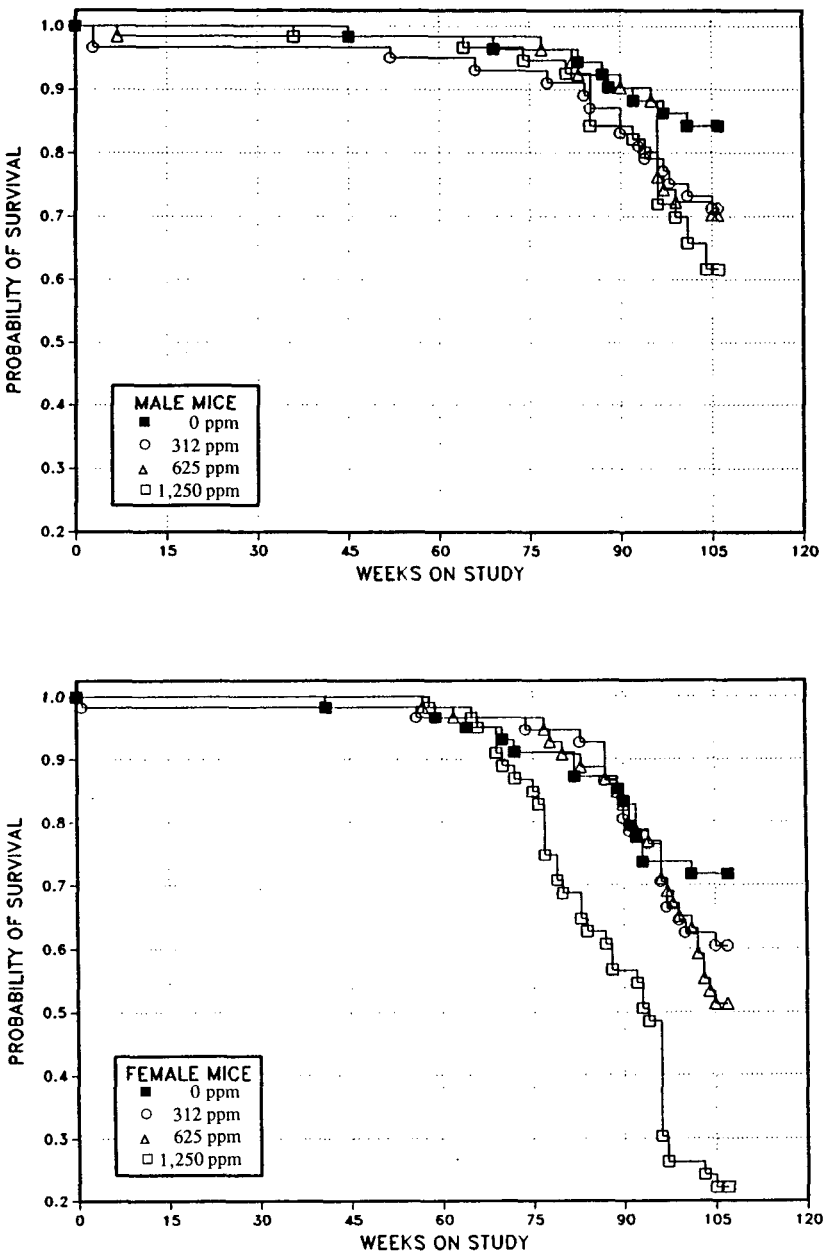


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 2 Years

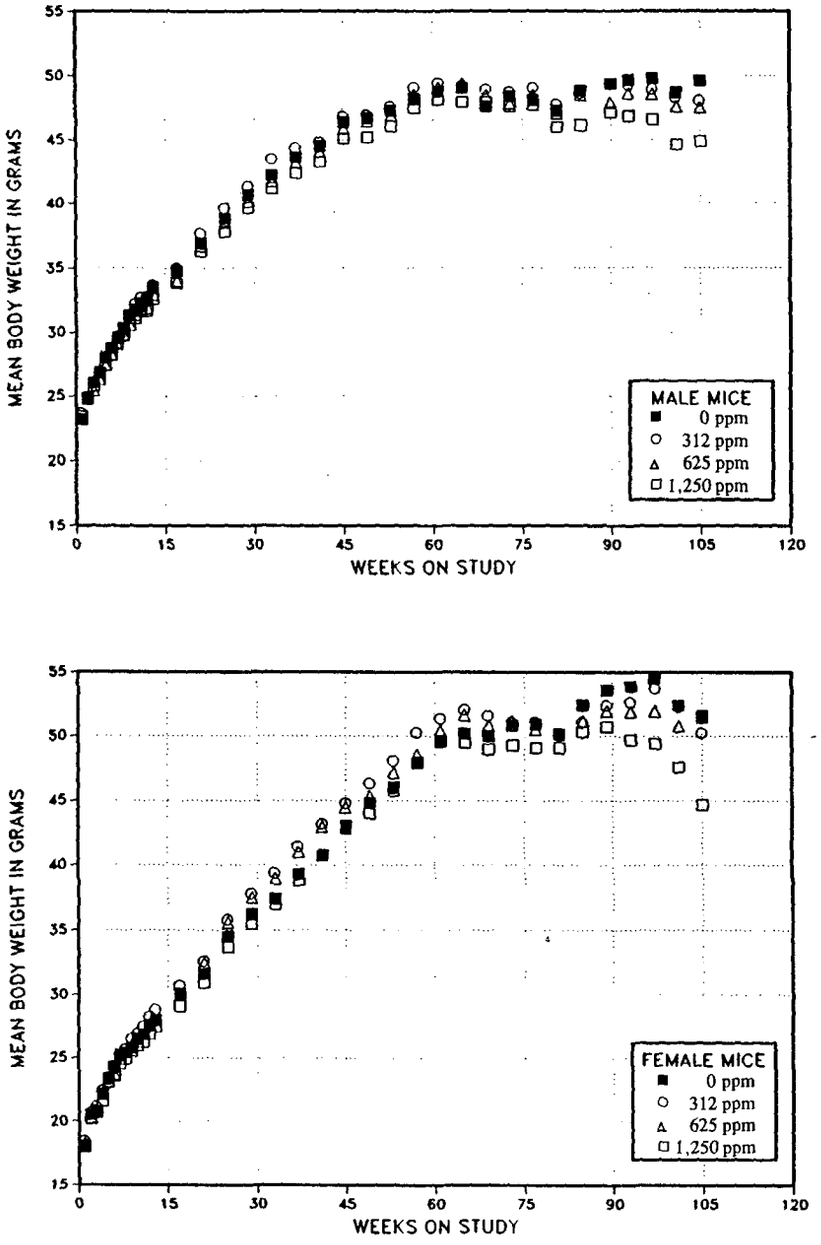


FIGURE 4
Growth Curves for Male and Female Mice Administered 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 2 Years

TABLE 23
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.2	60	23.7	102	60	23.2	100	60	23.4	101	60
2	24.9	60	24.9	100	60	24.8	100	60	24.7	99	60
3	26.1	60	26.0	100	59	25.4	97	60	25.8	99	60
4	26.8	60	26.9	100	58	26.4	99	60	26.3	98	60
5	28.1	60	28.0	100	58	27.4	98	60	27.5	98	60
6	28.8	60	28.7	100	58	28.3	98	60	28.2	98	60
7	29.6	60	29.6	100	58	29.1	98	59	29.1	98	60
8	30.3	60	30.1	99	58	29.8	98	59	29.7	98	60
9	31.4	60	31.2	99	58	30.6	98	59	30.6	98	60
10	31.8	60	32.2	101	58	31.4	99	59	31.1	98	60
11	32.2	60	32.7	102	58	31.8	99	59	31.6	98	60
12	32.6	60	32.8	101	58	31.9	98	59	31.7	97	60
13	33.5	60	33.7	101	58	32.9	98	59	32.6	97	60
17	34.8	60	35.0	101	58	34.0	98	59	33.8	97	60
21	36.9	60	37.7	102	58	36.7	100	59	36.3	98	60
25	38.8	60	39.6	102	58	38.5	99	59	37.8	97	60
29	40.7	60	41.3	102	58	40.1	99	59	39.7	98	60
33	42.2	60	43.5	103	58	41.7	99	59	41.2	98	60
37	43.6	60	44.4	102	58	43.2	99	59	42.4	97	59
41	44.5	60	44.8	101	58	44.1	99	59	43.3	97	59
45	46.4	59	46.8	101	58	45.9	99	59	45.1	97	59
49	46.7	59	46.9	100	58	46.5	100	59	45.2	97	59
53	47.3	59	47.6	101	57	46.9	99	59	46.1	98	59
57	48.2	59	49.1	102	57	48.5	101	59	47.5	99	59
61	48.8	59	49.4	101	57	49.1	101	59	48.1	99	59
65	49.0	59	49.2	100	57	49.4	101	59	48.0	98	57
69[a]	47.6	49	48.9	103	47	48.5	102	49	47.9	101	47
73	48.4	48	48.7	101	47	47.8	99	49	47.6	98	47
77	48.1	48	49.1	102	47	48.5	101	49	47.7	99	46
81	47.3	48	47.8	101	46	47.1	100	48	46.0	97	46
85	48.8	47	48.7	100	45	48.5	99	46	46.2	95	44
90	49.4	45	49.3	100	42	47.9	97	46	47.2	96	41
93	49.7	44	49.3	99	41	48.6	98	45	46.9	94	40
97	49.8	43	48.9	98	40	48.6	98	38	46.6	94	35
101	48.7	43	48.3	99	38	47.6	98	36	44.6	92	33
105	49.6	42	48.1	97	36	47.5	96	36	44.9	91	30
Mean for weeks											
1-13	29.2		29.3	100		28.7	98		28.6	98	
14-52	41.6		42.2	101		41.2	99		40.5	97	
53-105	48.6		48.7	100		48.2	99		46.8	96	

[a] Interim evaluation occurred during week 66.

TABLE 24
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	312 ppm Av. Wt. (g)	312 ppm Wt. (% of controls)	312 ppm No. of Survivors	625 ppm Av. Wt. (g)	625 ppm Wt. (% of controls)	625 ppm No. of Survivors	1,250 ppm Av. Wt. (g)	1,250 ppm Wt. (% of controls)	1,250 ppm No. of Survivors
1	18.0	60	18.5	103	60	18.3	102	60	18.1	101	60
2	20.5	60	20.7	101	60	20.3	99	60	20.2	99	60
3	20.9	60	21.2	101	60	20.9	100	60	20.7	99	60
4	22.1	60	22.4	101	60	22.2	101	60	21.6	98	60
5	23.4	60	23.5	100	60	23.1	99	60	23.0	98	60
6	24.3	60	24.1	99	60	23.7	98	60	23.5	97	60
7	25.2	60	25.2	100	60	24.9	99	60	24.5	97	60
8	25.4	60	25.7	101	60	25.4	100	60	24.9	98	60
9	25.7	60	26.5	103	60	25.9	101	60	25.5	99	60
10	26.5	60	26.9	102	60	26.5	100	60	26.0	98	60
11	26.8	60	27.5	103	60	26.9	100	60	26.2	98	60
12	27.6	60	28.3	103	60	27.6	100	60	26.8	97	60
13	28.0	60	28.8	103	60	28.0	100	60	27.5	98	60
17	30.1	60	30.7	102	60	29.9	99	60	29.1	97	60
21	31.6	60	32.6	103	60	32.5	103	60	30.9	98	60
25	34.5	60	35.8	104	60	35.6	103	60	33.7	98	60
29	36.2	60	37.8	104	60	37.5	104	60	35.5	98	60
33	37.4	60	39.4	105	60	39.0	104	60	37.0	99	60
37	39.3	60	41.5	106	60	41.1	105	60	38.9	99	60
41	40.7	60	43.2	106	60	43.0	106	60	40.7	100	60
45	42.8	59	44.8	105	60	44.5	104	60	43.0	101	60
49	44.8	59	46.3	103	60	45.4	101	60	44.0	98	60
53	46.0	59	48.1	105	60	47.2	103	60	45.8	100	60
57	48.0	59	50.3	105	59	48.6	101	60	47.9	100	60
61	49.6	58	51.4	104	59	50.4	102	59	49.6	100	59
65	50.2	57	52.1	104	59	51.7	103	58	49.5	99	58
69[a]	50.0	49	51.6	103	49	50.9	102	49	49.0	98	46
73	50.8	47	51.1	101	49	51.2	101	49	49.3	97	43
77	50.9	47	51.1	100	48	50.5	99	48	49.1	97	39
81	50.2	47	50.0	100	48	50.2	100	46	49.1	98	34
85	52.4	45	51.1	98	47	51.2	98	45	50.3	96	31
89	53.6	44	52.4	98	44	52.0	97	44	50.7	95	28
93	53.9	38	52.6	98	40	51.9	96	40	49.7	92	27
97	54.5	38	53.7	99	36	51.9	95	36	49.4	91	14
101	52.4	37	52.3	100	32	50.8	97	33	47.6	91	13
105	51.6	37	50.3	98	31	51.5	100	26	44.7	87	12
Mean for weeks											
1-13	24.2		24.6	102		24.1	100		23.7	98	
14-52	37.5		39.1	104		38.7	103		37.0	99	
53-105	51.0		51.3	101		50.7	99		48.7	96	

[a] Interim evaluation occurred during week 66.

Pathology and Statistical Analysis

This section describes statistically significant and biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the harderian gland, lung, skin, kidney, forestomach, and mammary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of 5% in at least one exposure group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Harderian Gland: The incidences of harderian gland adenoma in male and female mice exposed to 625 and 1,250 ppm were significantly greater than those in the control groups (Tables 25, C3, and D3). The incidence of harderian gland carcinoma in 1,250 ppm females was significantly greater than that in the control group (Tables 25 and D3). In 625 and 1,250 ppm males, and in all female exposure groups, the incidences of adenoma or carcinoma (combined) were significantly greater than those in the control groups (Tables 25, C3, and D3). In males exposed to 1,250 ppm, many of these neoplasms were bilateral (Tables 25 and C1). The incidences of adenoma and carcinoma in 625 and 1,250 ppm males and exposed females exceeded the NTP historical control range (Tables 25, C4a, and D4a). The majority of the harderian gland neoplasms were observed grossly at necropsy; in some instances these neoplasms were the primary reason for the moribund condition of the animals. Adenomas were expansile masses that had a variable growth pattern consisting of acini and cystic glands with papillary and solid areas. Carcinomas were more invasive, often with focal fibrosis. There was cellular pleomorphism, and, in some carcinomas, neoplastic cells had large cytoplasmic vacuoles. Metastases of carcinomas to the lung and other sites occurred in exposed and control groups of male and female mice (Plate 8). At the 15-month interim evaluation, the incidences of adenoma of the harderian gland in 1,250 ppm males and females were slightly greater than those in the control groups, but these differences were not statistically significant (Tables 25, C3, and D3). At 2 years, the incidences of hyperplasia in exposed male and females did not differ significantly from those in the control groups (Tables 25, C5, and D5).

TABLE 25
Incidence of Neoplasms and Nonneoplastic Lesions of the Harderian Gland in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Harderian Gland[a]	4	6	5	4
Hyperplasia[b]	0	0	1 (2.0)[c]	1 (3.0)
Adenoma	0	0	1	2
2-Year Study				
Harderian Gland	22	25	28	32
Hyperplasia	0	1 (3.0)	1 (2.0)	2 (2.0)
Adenoma				
Overall rate[d]	3/50 (6%)	6/51 (12%)	12/50 (24%)	18/49 (37%)
Adjusted rate[e]	7.1%	15.6%	31.0%	47.5%
Terminal rate[f]	3/42 (7%)	4/36 (11%)	9/35 (26%)	11/30 (37%)
First incidence (days)	736 (T)	656	669	565
Logistic regression test[g]	P<0.001	P=0.213	P=0.010	P<0.001
Adenoma, Bilateral				
Overall rate	0/50 (0%)	0/51 (0%)	1/50 (2%)	8/49**(16%)
Carcinoma				
Overall rate	1/50 (2%)	1/51 (2%)	4/50 (8%)	4/49 (8%)
Adjusted rate	2.3%	2.8%	10.1%	10.9%
Terminal rate	0/42 (0%)	1/36 (3%)	2/35 (6%)	1/30 (3%)
First incidence (days)	674	736 (T)	666	589
Logistic regression test	P=0.071	P=0.762	P=0.182	P=0.187
Adenoma or Carcinoma[h]				
Overall rate	4/50 (8%)	7/51 (14%)	16/50 (32%)	22/49 (45%)
Adjusted rate	9.3%	18.2%	39.4%	54.3%
Terminal rate	3/42 (7%)	5/36 (14%)	11/35 (31%)	12/30 (40%)
First incidence (days)	674	656	666	565
Logistic regression test	P<0.001	P=0.233	P=0.003	P<0.001

(continued)

TABLE 25
Incidence of Neoplasms and Nonneoplastic Lesions of the Harderian Gland in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Harderian Gland	4	5	4	7
Hyperplasia	0	0	1 (1.0)	1 (3.0)
Adenoma	1	1	0	4
2-Year Study				
Harderian Gland	18	27	27	33
Hyperplasia	1 (3.0)	1 (1.0)	2 (1.5)	0
Adenoma				
Overall rate	2/52 (4%)	6/50 (12%)	8/51 (16%)	15/50 (30%)
Adjusted rate	4.3%	17.7%	23.7%	55.7%
Terminal rate	0/37 (0%)	3/30 (10%)	4/26 (15%)	3/11 (27%)
First incidence (days)	447	669	557	551
Logistic regression test	P<0.001	P=0.125	P=0.040	P<0.001
Carcinoma				
Overall rate	1/52 (2%)	6/50 (12%)	5/51 (10%)	7/50 (14%)
Adjusted rate	2.5%	17.6%	16.1%	25.0%
Terminal rate	0/37 (0%)	4/30 (13%)	3/26 (12%)	0/11 (0%)
First incidence (days)	646	627	669	575
Logistic regression test	P=0.095	P=0.052	P=0.098	P=0.033
Adenoma or Carcinoma[i]				
Overall rate	3/52 (6%)	12/50 (24%)	13/51 (25%)	19/50 (38%)
Adjusted rate	6.7%	33.3%	37.5%	64.2%
Terminal rate	0/37 (0%)	7/30 (23%)	7/26 (27%)	3/11 (27%)
First incidence (days)	447	627	557	551
Logistic regression test	P<0.001	P=0.010	P=0.006	P=0.002

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with harderian gland examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 80/1,474 (5.4% ± 4.5%); range 0%-20%
[i] Historical incidence: 59/1,470 (4.0% ± 3.1%); range 0%-10%

Lung: The incidences of alveolar/bronchiolar adenoma and of alveolar/bronchiolar adenoma or carcinoma (combined) in 1,250 ppm males and females and 625 ppm females were significantly greater than those in the control groups (Tables 26, C3, and D3). In males exposed to 1,250 ppm, the incidences of multiple adenoma and of alveolar/bronchiolar carcinoma were significantly greater than those in the control group (Tables 26 and C1). The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 625 and 1,250 ppm males and females exceeded the NTP historical control range (Tables 26, C4b, and D4b).

The majority of these neoplasms were visible grossly as white or gray nodules in the lung. The morphology of the lung neoplasms was similar in control and exposed groups. Carcinomas had variable growth patterns, increased cellular pleomorphism, increased numbers of mitoses and evidence of local invasion (Plate 9). In one male and one female in the 625 ppm groups and in one male in the 1,250 ppm group, carcinomas had foci of metastases in lymph nodes, liver, and other sites.

At 15 months, the incidences of alveolar/bronchiolar neoplasms and alveolar epithelial hyperplasia in exposed mice were not significantly different from those in the control groups (Tables 26, C1, C5, D1, and D5). At 2 years, the incidences of alveolar epithelial hyperplasia in 625 and 1,250 ppm females were significantly greater than that in the control group (Tables 26, C5, and D5).

TABLE 26
Incidence of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Lung[a]	10	9	10	10
Alveolar Epithelium, Hyperplasia[b]	1 (1.0)[c]	0	1 (1.0)	3 (1.3)
Alveolar/bronchiolar Adenoma	2	1	4	0
Alveolar/bronchiolar Carcinoma	0	0	0	1
2-Year Study				
Lung	50	51	50	49
Alveolar Epithelium, Hyperplasia	6 (1.5)	7 (2.1)	5 (2.0)	8 (2.0)
Alveolar/bronchiolar Adenoma (Single and Multiple)				
Overall rate[d]	12/50 (24%)	4/51 (8%)	12/50 (24%)	21/49 (43%)
Adjusted rate[e]	27.1%	10.3%	30.6%	57.6%
Terminal rate[f]	10/42 (24%)	3/36 (8%)	9/35 (26%)	15/30 (50%)
First incidence (days)	478	586	536	593
Logistic regression test[g]	P=0.001	P=0.030N	P=0.589	P=0.020
Alveolar/bronchiolar Adenoma, Multiple				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	10/49** (20%)
Alveolar/bronchiolar Carcinoma (Single and Multiple)				
Overall rate	3/50 (6%)	7/51 (14%)	8/50 (16%)	11/49 (22%)
Adjusted rate	7.1%	18.7%	19.9%	33.5%
Terminal rate	3/42 (7%)	6/36 (17%)	5/35 (14%)	9/30 (30%)
First incidence (days)	736 (T)	646	572	641
Logistic regression test	P=0.011	P=0.130	P=0.098	P=0.009
Alveolar/bronchiolar Carcinoma, Multiple				
Overall rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/49 (6%)
Alveolar/bronchiolar Adenoma or Carcinoma[h]				
Overall rate	15/50 (30%)	11/51 (22%)	16/50 (32%)	25/49 (51%)
Adjusted rate	33.9%	28.4%	38.9%	66.9%
Terminal rate	13/42 (31%)	9/36 (25%)	11/35 (31%)	18/30 (60%)
First incidence (days)	478	586	536	593
Logistic regression test	P=0.003	P=0.280N	P=0.491	P=0.011

(continued)

TABLE 26
Incidence of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Lung	8	10	9	10
Alveolar Epithelium, Hyperplasia	1 (1.0)	0	0	0
Alveolar/bronchiolar Adenoma	1	0	0	2
Alveolar/bronchiolar Carcinoma	1	0	0	0
2-Year Study				
Lung	52	50	51	50
Alveolar Epithelium, Hyperplasia	1 (1.0)	3 (1.3)	8** (1.5)	15** (1.9)
Alveolar/bronchiolar Adenoma (Single and Multiple)				
Overall rate	3/52 (6%)	3/50 (6%)	9/51 (18%)	17/50 (34%)
Adjusted rate	7.7%	8.8%	29.1%	64.2%
Terminal rate	2/37 (5%)	2/30 (7%)	5/26 (19%)	4/11 (36%)
First incidence (days)	640	619	669	534
Logistic regression test	P<0.001	P=0.642	P=0.048	P<0.001
Alveolar/bronchiolar Adenoma, Multiple				
Overall rate	1/52 (2%)	0/50 (0%)	2/51 (4%)	2/50 (4%)
Alveolar/bronchiolar Carcinoma (Single and Multiple)				
Overall rate	2/52 (4%)	2/50 (4%)	6/51 (12%)	5/50 (10%)
Adjusted rate	5.3%	6.7%	17.6%	33.9%
Terminal rate	1/37 (3%)	2/30 (7%)	3/26 (12%)	2/11 (18%)
First incidence (days)	705	743 (T)	428	669
Logistic regression test	P=0.048	P=0.659	P=0.125	P=0.094
Alveolar/bronchiolar Carcinoma, Multiple				
Overall rate	0/52 (0%)	0/50 (0%)	1/51 (2%)	1/50 (2%)
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	5/52 (10%)	5/50 (10%)	15/51 (29%)	19/50 (38%)
Adjusted rate	12.7%	15.3%	43.4%	71.9%
Terminal rate	3/37 (8%)	4/30 (13%)	8/26 (31%)	5/11 (45%)
First incidence (days)	640	619	428	534
Logistic regression test	P<0.001	P=0.597	P=0.011	P<0.001

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lung examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal. A lower incidence in an exposure group is indicated by N.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 265/1,469 (18.0% ± 7.6%); range 4%-32%
[i] Historical incidence: 110/1,469 (7.5% ± 5.0%); range 2%-26%

Skin: The incidence of subcutaneous tissue sarcoma and the combined incidences of fibrosarcoma or sarcoma in 1,250 ppm female mice were significantly greater than those in the controls (Tables 27 and D3). Malignant mesenchymal neoplasms of the skin occurred in 24% of the females exposed to 1,250 ppm. The incidences of fibrosarcoma or sarcoma (combined) in 1,250 ppm females exceeded the NTP historical control range (Tables 27 and D4c). There was variation in morphology within and between these neoplasms (Plates 10 and 11). Most consisted of spindle-shaped or pleomorphic or vacuolated cells forming irregular, interwoven patterns or areas with intercellular edema.

TABLE 27
Incidence of Neoplasms of the Subcutaneous Tissue of the Skin in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Skin[a]	52	50	51	50
Subcutaneous Tissue, Schwannoma, Malignant[b]	0	1	0	0
Subcutaneous Tissue, Fibrosarcoma	0	0	0	1
Subcutaneous Tissue, Sarcoma	0	1	4	11**
Subcutaneous Tissue, Fibrosarcoma or Sarcoma[c]	0	1	4	12**

** Significantly different ($P \leq 0.01$) from the control group by the logistic regression test
[a] Number of animals with skin examined microscopically
[b] Number of animals with neoplasm
[c] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 21/1,470 (1.4% ± 2.2%); range 0%-8%

Kidney: Marginally increased in incidences of renal tubule adenoma were observed in 625 and 1,250 ppm male mice (0/49, 0/51, 3/50, 2/49; Table C1). These incidences exceeded the NTP historical control range for this neoplasm (Table C4c). In three of the five male mice with adenomas, the adenomas were observed grossly at necropsy. Adenomas were all expansile, well-differentiated tumors with tubular and glandular patterns (Plate 12). Focal renal tubule hyperplasia was present in two males from the 1,250 ppm group (Table C5).

Forestomach: The incidences of squamous cell papilloma of the forestomach in 625 and 1,250 ppm female mice were significantly greater than that in the control group (Tables 28 and D3). In 1,250 ppm males, the incidence of squamous cell papilloma or squamous cell carcinoma (combined) was significantly greater than that in the control group (Tables 28 and C3). In addition, papillomas also occurred in one male and one female in the 1,250 ppm groups at the 15-month interim evaluation. The incidences of squamous cell adenoma or squamous cell carcinoma (combined) in exposed male mice were at or slightly greater than the upper limit of the NTP historical control range (0%-6%; Table C4d). The papillomas were well-differentiated, benign neoplasms consisting of multiple fronds of a squamous epithelium supported by delicate fibrovascular stroma. Squamous cell carcinomas, which were present in two 1,250 ppm males, were invasive malignant neoplasms; one carcinoma metastasized to the lung as well as other abdominal organs (Table C1).

TABLE 28
Incidence of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
15-Month Interim Evaluation				
Forestomach[a]	10	9	10	10
Mucosa, Hyperplasia[b]	0	0	1 (3.0)[c]	0
Squamous Cell Papilloma	0	0	0	1
2-Year Study				
Forestomach	49	51	50	48
Mucosa, Hyperplasia	4 (1.5)	1 (1.0)	3 (2.0)	4 (2.0)
Squamous Cell Papilloma				
Overall rate[d]	0/50 (0%)	3/51 (6%)	2/50 (4%)	2/49 (4%)
Adjusted rate[e]	0.0%	8.0%	5.7%	6.7%
Terminal rate[f]	0/42 (0%)	2/36 (6%)	2/35 (6%)	2/30 (7%)
First incidence (days)	—[h]	683	736 (T)	736 (T)
Logistic regression test[g]	P=0.262	P=0.112	P=0.199	P=0.168
Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/51 (0%)	1/50 (2%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	2.9%	5.9%
Terminal rate	0/42 (0%)	0/36 (0%)	1/35 (3%)	1/30 (3%)
First incidence (days)	—	—	736 (T)	669
Logistic regression test	P=0.061	—	P=0.464	P=0.226
Squamous Cell Papilloma or Squamous Cell Carcinoma[i]				
Overall rate	0/50 (0%)	3/51 (6%)	3/50 (6%)	4/49 (8%)
Adjusted rate	0.0%	8.0%	8.6%	12.4%
Terminal rate	0/42 (0%)	2/36 (6%)	3/35 (9%)	3/30 (10%)
First incidence (days)	—	683	736 (T)	669
Logistic regression test	P=0.053	P=0.112	P=0.091	P=0.047

(continued)

TABLE 28
Incidence of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
15-Month Interim Evaluation				
Forestomach	8	10	9	10
Mucosa, Hyperplasia	1 (1.0)	0	3 (2.0)	3 (2.3)
Squamous Cell Papilloma	0	0	0	1
2-Year Study				
Forestomach	51	50	51	49
Mucosa, Hyperplasia	9 (2.0)	5 (2.2)	13 (1.8)	6 (2.0)
Squamous Cell Papilloma[j]				
Overall rate	0/52 (0%)	1/50 (2%)	5/51 (10%)	3/50 (6%)
Adjusted rate	0.0%	2.4%	16.6%	24.0%
Terminal rate	0/37 (0%)	0/30 (0%)	3/26 (12%)	2/11 (18%)
First incidence (days)	—	625	639	677
Logistic regression test	P=0.022	P=0.504	P=0.029	P=0.028

(T)Terminal sacrifice
[a] Number of animals with forestomach examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to the pairwise comparisons between the controls and that exposure group. The logistic regression test regards these lesions as nonfatal.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 22/1,474 (1.5% ± 2.0%); range 0%-6%
[j] Historical incidence: 31/1,470 (2.1% ± 2.9%); range 0%-14%

Mammary Gland: The incidences of carcinoma of the mammary gland were slightly increased in 625 and 1,250 ppm female mice (0/50, 0/50, 1/50, 3/49; Table D1). An adenoacanthoma was also present in one 1,250 ppm female (Table D1). One of the female mice from the 1,250 ppm group had multiple carcinomas; however, the incidence of these mammary gland neoplasms was within the NTP historical control range (Table D4e).

Other: The incidence of hemangioma or hemangiosarcoma (combined) was significantly increased in 1,250 ppm female mice (1/52, 2/50, 0/51, 5/50; Tables D1 and D3) and was slightly increased in 312 and 1,250 ppm males (2/50, 6/51, 0/50, 5/49; Tables C1 and C3). In male mice there was no dose response and the highest incidence was well within the historical control range. In females, the highest incidence slightly exceeded the historical control range (Table D4f). The neoplasms occurred at various sites (bone marrow, colon, kidney, liver, mesentery, spleen, subcutis, testes, urinary bladder, and uterus) in both exposed and control mice. The morphology of benign and malignant vascular tumors was similar between exposed and control groups.

GENETIC TOXICOLOGY

2,2-Bis(bromomethyl)-1,3-propanediol was shown to be mutagenic *in vitro* and *in vivo*, but the conditions required to observe the positive responses were highly specific, and 2,2-bis(bromomethyl)-1,3-propanediol was not active in all assays. In the two *Salmonella* assays reported here (Table E1), 2,2-bis(bromomethyl)-1,3-propanediol gave a positive response only in the second assay (Zeiger *et al.*, 1992), which used a different concentration of S9 from the first assay (Mortelmans *et al.*, 1986). Metabolic activation, specifically in the form of 30% Aroclor 1254-induced male Syrian hamster liver S9, was required to obtain the mutagenic response; 10% hamster S9 was ineffective, as was 10% or 30% S9 derived from livers of pretreated rats. No other *Salmonella* strain/activation combination was responsive to the effects of 2,2-bis(bromomethyl)-1,3-propanediol.

In cytogenetic tests with cultured Chinese hamster ovary cells (Galloway *et al.*, 1987), 2,2-bis(bromomethyl)-1,3-propanediol did not induce sister chromatid exchanges, with or without S9 (Table E2), but a dose-related increase in chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated in the presence of induced rat liver S9 (Table E3). Both tests were conducted up to doses which induced marked cytotoxicity; cell confluence in the sister chromatid exchange test was reduced 75% at the top dose tested with S9 (1,200 μg/mL). A majority of the breaks which were observed in the aberration assay were located in the heterochromatic region of the long arm of the X chromosome. The reason for this preferential breakage site is not known. Also, the type of damage pattern seen with 2,2-bis(bromomethyl)-1,3-propanediol (induction of chromosomal aberrations but not sister chromatid exchanges) is unusual. Most chemicals which induce chromosomal aberrations also induce sister chromatid exchanges (Galloway *et al.*, 1987).

2,2-Bis(bromomethyl)-1,3-propanediol was also shown to be genotoxic *in vivo*. Significant increases in micronucleated normochromatic erythrocytes were observed in peripheral blood samples obtained from male and female mice exposed for 13 weeks to 2,2-bis(bromomethyl)-1,3-propanediol in feed (Table E6). These increases were observed in the two highest dose groups of male mice (5,000 and 10,000 ppm) and the three highest dose groups of female mice (2,500, 5,000, and 10,000 ppm).

In the first of two mouse bone marrow micronucleus tests performed to confirm the positive results seen in the 13-week feed study, inconsistent results were obtained between two trials which used the same dose range of 100 to 400 mg/kg 2,2-bis(bromomethyl)-1,3-propanediol, administered by gavage three times at 24-hour intervals (Table E4). Results of the first trial were negative; however, in the second trial, 2,2-bis(bromomethyl)-1,3-propanediol produced a clear, dose-related increase in micronucleated polychromatic erythrocytes. Because the positive response was not reproduced, the results were concluded to be equivocal.

In an attempt to clarify the results obtained in the first bone marrow micronucleus test, a second investigation was performed using both male and female mice. 2,2-Bis(bromomethyl)-1,3-propanediol was administered as a single intraperitoneal injection (150 to 600 mg/kg) and bone marrow samples were taken 48 hours after dosing. The results of this experiment, shown in Table E5, provide evidence of the ability of 2,2-bis(bromomethyl)-1,3-propanediol to induce micronuclei in bone marrow cells of female mice. Although male mice in all three dose groups showed a two-fold increase in the frequency of micronucleated polychromatic erythrocytes, the trend test was not significant due to the similarity in the responses, and pairwise analyses were also insignificant. The response in female mice was somewhat stronger (2.5-fold increase over background, at the highest dose) and was directly related to increasing doses of 2,2-bis(bromomethyl)-1,3-propanediol. These results were consistent with the stronger response observed in female mice in the 13-week feed study (Table E4).

In conclusion, 2,2-bis(bromomethyl)-1,3-propanediol was genotoxic *in vitro* and *in vivo*, inducing gene mutations in *Salmonella* strain TA100, chromosomal aberrations in cultured Chinese hamster ovary cells, and micronuclei in erythrocytes of male and female mice. The *in vitro* responses required S9.

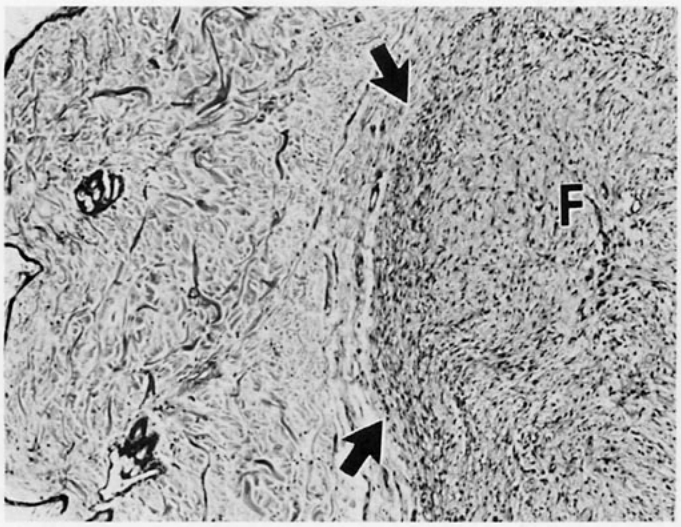


PLATE 1
Fibroma in skin of male F344/N rat administered 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 13 weeks in a stop-exposure group and necropsied at week 95. Well-differentiated fibroma (F) comprised of densely packed spindle cells is clearly demarcated (arrows) from the adjacent normal dermis; skin surface is at far left. H&E 65×

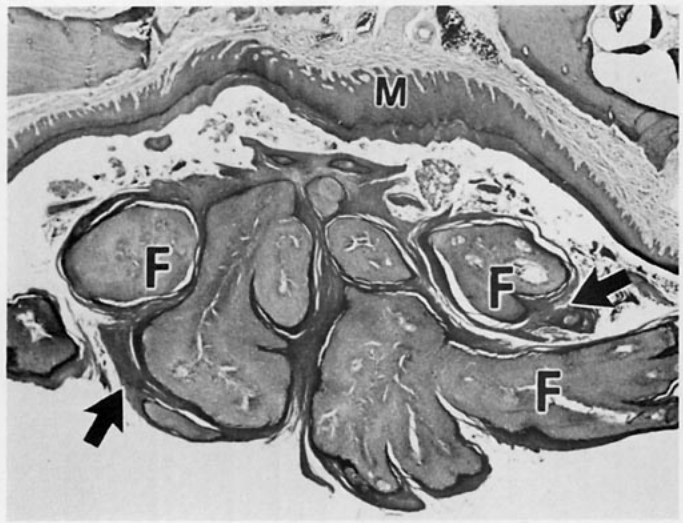


PLATE 2
Squamous cell papilloma in the dorsal posterior portion of the pharynx (hard palate) of a male F344/N rat administered 2,500 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. This exophytic mass arising from the oral cavity mucosa (M) consists of prominent papillary fronds (F) of well-differentiated squamous epithelium covered by a layer of keratin (arrows). H&E 25×

PLATE 3
Squamous cell papilloma in the forestomach of a male F344/N rat administered 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. Note the absence of inflammation or hyperplasia in adjacent forestomach mucosa (arrows). H&E 40×

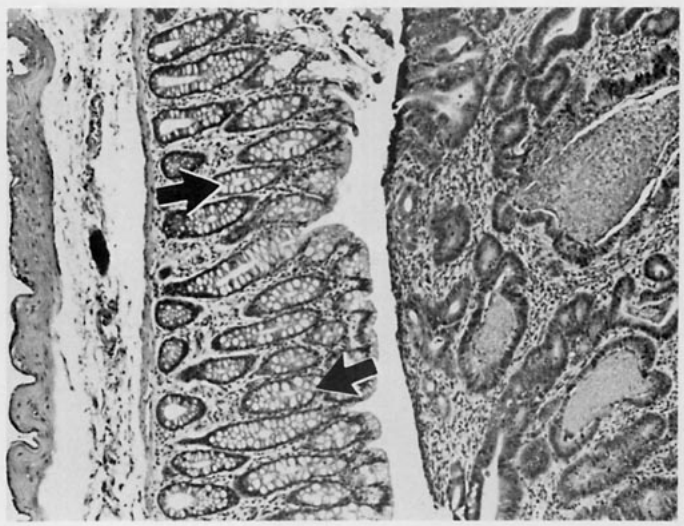


PLATE 4
Adenoma of the colon in a male F344/N rat administered 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. Large tumor mass (right) fills lumen of colon and is comprised of dilated glands lined by a closely packed tall columnar epithelium that lacks the goblet cell differentiation which is present in normal colonic mucosa (arrows). H&E 65×

PLATE 5
Mesothelioma attached to the capsular surface of the testis (arrows) in a male F344/N rat administered 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 13 weeks in a stop-exposure study and necropsied at week 75. Tumor arising from tunica vaginalis consists of densely cellular solid areas with formation of papillary structures. H&E 30×

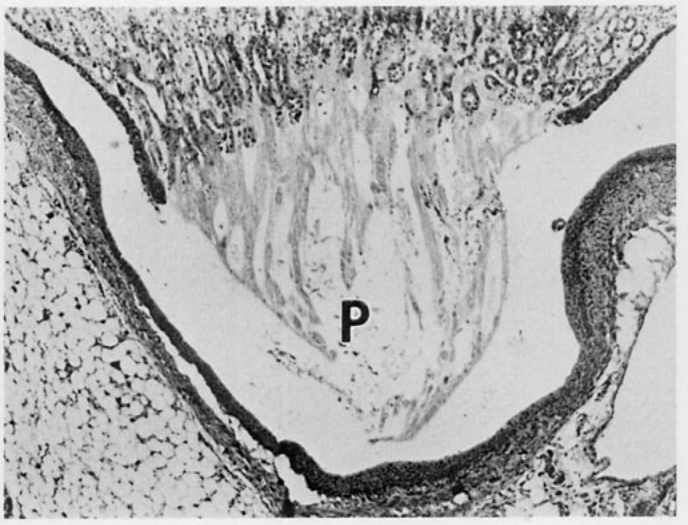


PLATE 6
Papillary degeneration and necrosis of the tip of the renal papilla (P) in a female F344/N rat administered 10,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. There is necrosis of the urothelium and stroma in the distal portion of the papilla. H&E 40×

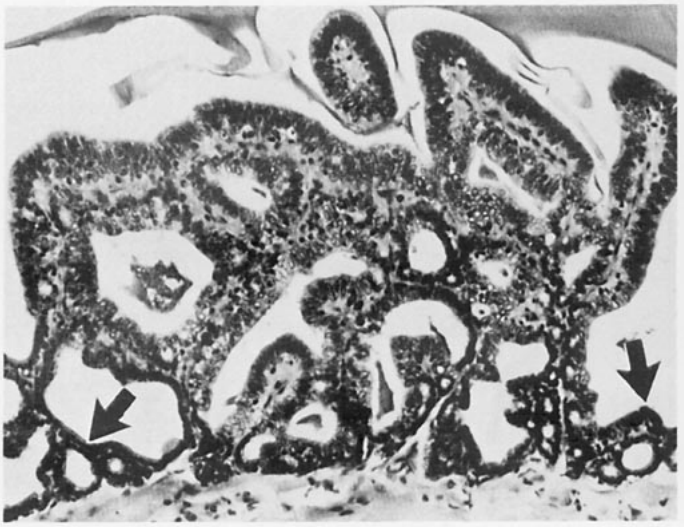


PLATE 7
Focal hyperplasia in seminal vesicle of male F344/N rat administered 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 13 weeks in a stop-exposure study and necropsied at week 75. Note increased height and crowding of hyperplastic epithelium compared to the cells in the normal adjacent mucosa (arrows). H&E 160×

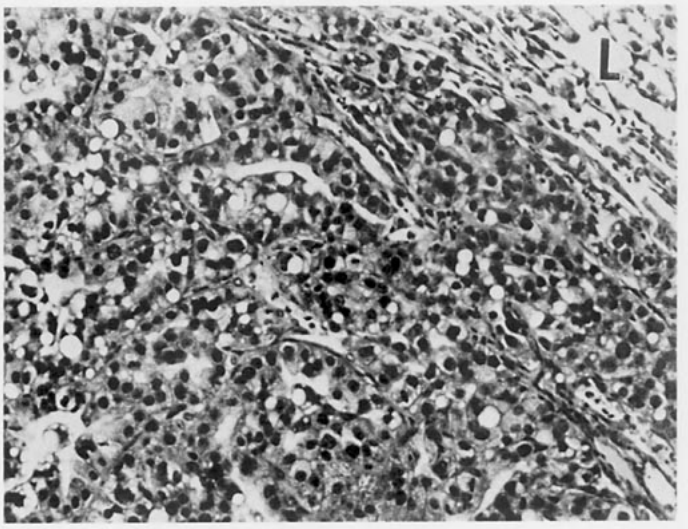


PLATE 8
Harderian gland carcinoma in a female B6C3F$_1$ mouse administered 312 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. Neoplastic cells with foamy to vacuolated cytoplasm form a glandular or acinar pattern in this tumor which has metastasized to the lung (L). H&E 160×

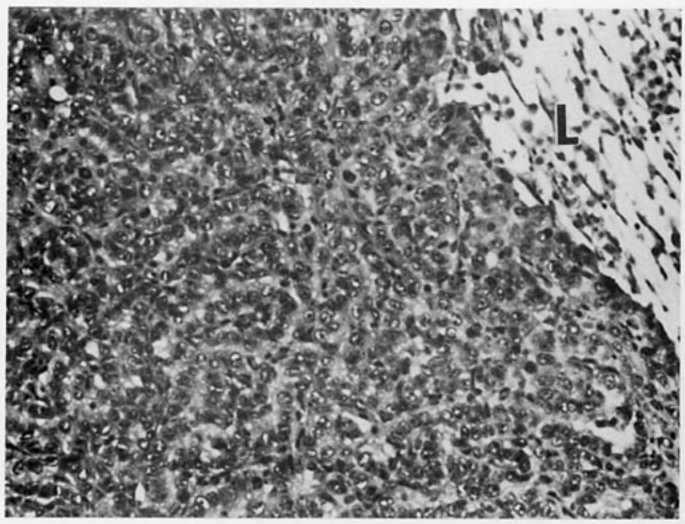


PLATE 9
Alveolar/bronchiolar carcinoma in lung of male B6C3F$_1$ mouse administered 1,250 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. Neoplastic cuboidal epithelium forms a densely packed glandular pattern that is compressing alveoli of adjacent lung (L). H&E 160×

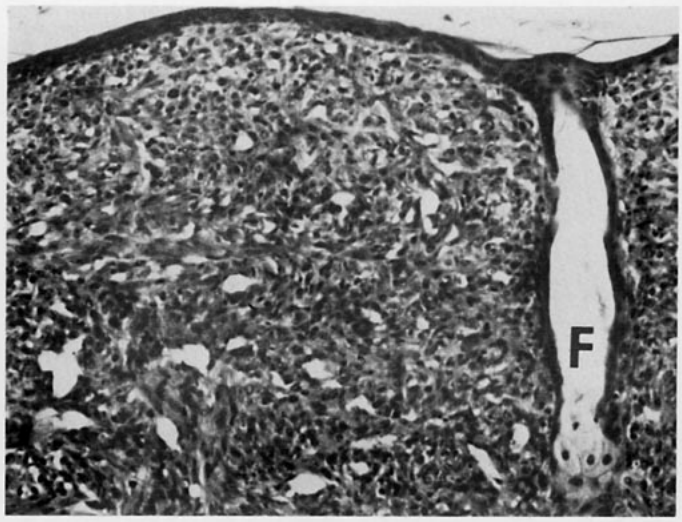


PLATE 10
Sarcoma in dermis of female B6C3F$_1$ mouse administered 1,250 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 2 years. A few remaining hair follicles (F) and sebaceous glands are present in dermis which has been replaced by neoplastic mesenchymal cells. H&E 160×

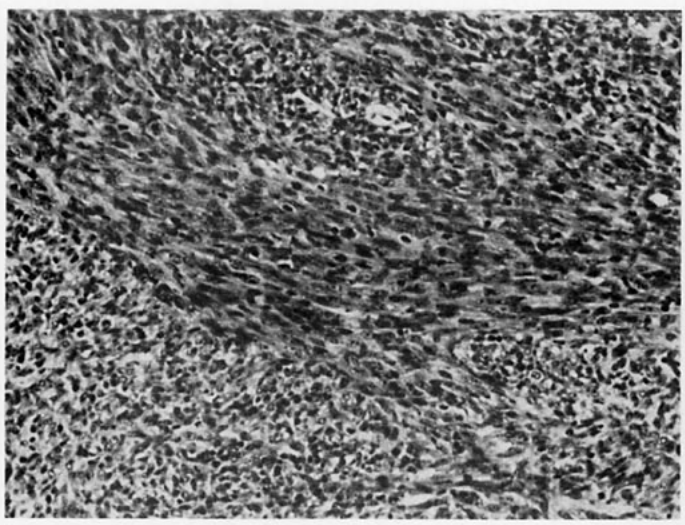


PLATE 11
Detail of another area of sarcoma shown in Plate 10 demonstrates pattern of interlacing bundles of neoplastic spindle cells. H&E 160×

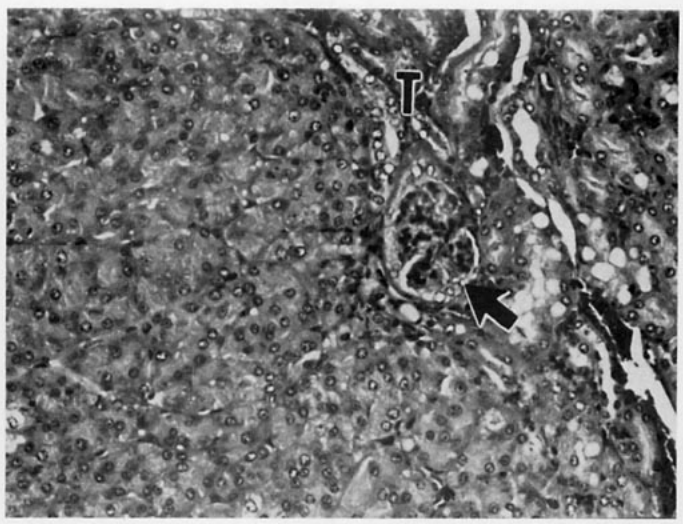


PLATE 12
Adenoma of renal tubule in male B6C3F$_1$ mouse consists of an expansile mass of well-differentiated neoplastic renal tubule epithelial cells compressing the normal cortical tubules (T) and glomerulus (arrow). H&E 160×

DISCUSSION AND CONCLUSIONS

These studies of 2,2-bis(bromomethyl)-1,3-propanediol [technical grade FR-1138®; 78.6% 2,2-bis(bromomethyl)-1,3-propanediol, 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane, 6.9% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane, 0.2% pentaerythritol, and 7.7% dimers and structural isomers] show that this flame retardant is a multi-site, multispecies carcinogen (Table 29).

In the 13-week feed studies, the high dose for rats was 20,000 ppm (estimated to deliver about 900 to 1,340 mg/kg) and for mice was 10,000 ppm (estimated to deliver 2,900 mg/kg). There were no treatment-related deaths, but mean body weights of male and female rats exposed to 5,000 ppm and above, of male mice exposed to 1,250 ppm and above, and of female mice exposed to 625 ppm and above were lower than those of the control groups.

Based on the results of clinical chemistry and histopathology, chemical related toxicity was evident in the kidney and urinary bladder of rats and mice. Urinalysis demonstrated the development of an isosthenuric polyuria in rats primarily in the 10,000 and 20,000 ppm exposure groups, indicating the kidneys had not altered the concentration of the glomerular filtrate. This change was less evident in females. The primary control of urine volume and tonicity occurs by antidiuretic hormone-influenced water resorption in the distal renal tubules and collecting ducts. There are renal and nonrenal causes of polyuria, including renal injury or disease, drugs (e.g., diuretics or aminoglycosides), increased water intake, decreased response to antidiuretic hormone, osmotic diuresis, and hyperadrenocorticism. In this study, minimal to mild renal papillary injury in rats may have contributed to altered distal tubular function resulting in the isosthenuric polyuria. However, water deprivation tests demonstrated that male and female rats were able to concentrate their urine in response to reduced water intake throughout the study. This indicates that the antidiuretic hormone-dependent pituitary-renal axis was still intact. In the mice, the clinical chemistry and urinalysis findings were slightly different from those in rats. There was no evidence of polyuria in the mice, but blood urea nitrogen was significantly increased in 10,000 ppm males and females. Blood urea nitrogen concentration is considered an insensitive biomarker of renal damage and requires approximately 75% of the nephrons to be nonfunctional before increased serum blood urea nitrogen concentration occurs (Finco, 1989). In this study, there were mild to moderate tubule and papillary changes, but the increased blood urea nitrogen may have also been secondary to increased protein catabolism related to the decreased body weight gain or body weight loss in 10,000 ppm mice.

Chemical-related lesions were observed only in the urinary bladder and kidney of rats and mice. Kidney lesions in mice (papillary necrosis and renal tubule regeneration and fibrosis) were more severe than those observed in rats (papillary degeneration). Urinary bladder lesions in the mice were also more severe than in rats. The presence of kidney and urinary bladder lesion in mice at exposure concentrations that were lower than those which caused similar but less severe lesions in rats would indicate that mice are more sensitive to the renal effects of 2,2-bis(bromomethyl)-1,3-propanediol in 13-week toxicity studies. Based on an equivalent dose per body weight, the toxic effects of 2,2-bis(bromomethyl)-1,3-propanediol on the urinary bladder and kidney of rats and mice were similar whether administered by gavage or in feed (Elwell *et al.*, 1989).

In rats and mice, no abnormalities were observed in sperm morphology, count, or motility or in the estrous cycle length. While body weights in exposed groups were lower than in the controls, diet restriction studies have shown that body weight effects alone (20% lower body weight) do not cause reproductive system toxicity in rats or mice (Chapin *et al.*, 1993).

In continuous breeding studies, 2,2-bis(bromomethyl)-1,3-propanediol has been shown to impair

fertility in female mice in the absence of an effect on reproductive organ weights or estrual cyclicity (Treinen *et al.*, 1989). The ovary may be a target for 2,2-bis(bromomethyl)-1,3-propanediol since 0.4% 2,2-bis (bromomethyl)-1,3-propanediol significantly decreased the number of primary and growing ovarian follicles in female mice (Heindel *et al.*, 1989). It should be noted that in these studies where ovarian toxicity occurred, 2,2-bis(bromomethyl)-1,3-propanediol exposure began *in utero*. In contrast, in the present 13-week and 2-year studies reported here, exposure did not begin until animals were 6 to 7 weeks of age, and ovarian toxicity was not observed.

The 2,2-bis(bromomethyl)-1,3-propanediol 2-year studies consisted of continuous-exposure studies in which the chemical was administered continuously to rats and mice in feed. In addition there was a stop-exposure study in male rats in which the animals received 20,000 ppm 2,2-bis(bromomethyl)-1,3-propanediol in feed for 3 months, and then received undosed feed for the remainder of the 2-year study.

2,2-Bis(bromomethyl)-1,3-propanediol administered in the feed caused early deaths in 10,000 ppm male and female rats, 1,250 ppm female mice, and 20,000 ppm stop-exposure male rats. These early deaths were attributed primarily to the carcinogenic effects of the chemical.

The incidences of skin tumors in male rats from the 5,000 and 10,000 ppm continuous-exposure groups and the 20,000 ppm stop-exposure group were significantly greater than those in the control group, and included increased incidences of squamous cell papilloma, keratoacanthoma, basal cell adenoma, sebaceous gland adenoma, and trichoepithelioma. The incidences of skin tumors in exposed female rats did not differ significantly from those in the control group. Other studies [e.g., benzidine congener dyes (NTP, 1990a, 1991a,b, 1992, and 1994a); 2,3-dibromo-1-propanol (NTP, 1994b)] have shown that genotoxic chemicals administered orally can cause skin tumors in rats, and the incidence for these tumors is generally greater in male rats than in female rats. The mechanism for this sex difference could not be determined from this study but may be due, in part, to metabolic differences between the sexes.

In the Zymbal's gland, a modified sebaceous gland, there was an increased incidence of neoplasms in male rats. The Zymbal's gland and skin are related epithelial tissues. In a review of NTP findings, 17 chemicals induced Zymbal's gland neoplasms, 14 induced skin neoplasms, and 11 induced neoplasms at both sites in rats. Most of the chemicals inducing Zymbal's gland and skin neoplasms also caused neoplasms at other sites. These chemicals are generally genotoxic in the *Salmonella* assay system, and chemically induced genetic damage is thought to be the underlying mechanism for development of skin and Zymbal's gland neoplasms (NTP, 1991a).

2,2-Bis(bromomethyl)-1,3-propanediol exposure increased the incidence of mammary gland neoplasms in rats. The treatment-related increase in mammary gland fibroadenoma was greater in female than in male rats. However, there was a significant increase in subcutaneous fibroma in exposed groups of male rats. Other chemicals which have caused an increase in the incidences of mammary gland neoplasms in female rats have also been associated with an increased incidences in fibroma (cytembena; NTP, 1981), fibroadenoma (glycidol; NTP, 1990b), or a combination of fibroma and fibroadenoma (methylene chloride; NTP, 1986c) in male rats. The chemicals that cause mammary gland neoplasms in rats are frequently genotoxic chemicals suggesting that genetic damage may contribute to this neoplastic response. Recent epidemiology studies have found an association between exposure to halogenated hydrocarbons and breast cancer in certain subsets of populations examined (Wolff *et al.*, 1993; Kreiger *et al.*, 1994).

There were treatment-related increased incidences of squamous cell neoplasms in the oral cavity (tongue and pharynx) and esophagus in male and female rats. In addition, there were treatment-related squamous cell neoplasms of the forestomach and adenoma and carcinoma of the small and large intestine in male rats. There was no evidence for toxicity at these sites in the 13-week studies or at the 15-month interim evaluation of the 2-year study. The presence of neoplasms in the gastrointestinal tract of exposed rats suggests that the chemical may interact directly with the mucosal epithelium. Although the increased incidence in intestinal neoplasms was limited to male rats, this effect was seen primarily in the stop-exposure group, which did not include females.

Other chemicals which have been found to cause oral cavity neoplasms in rats [including benzene (NTP, 1986a), benzidene-congener chemicals or dyes (NTP, 1990a, 1991a,b, 1992, and 1994a), glycidol (NTP, 1990b), trichloropropane (NTP, 1994c), 1,2-dibromo-3-chloropropane (NTP, 1982a), 2,3-dibromo-1-propanol (NTP, 1994b), and dimethylvinyl chloride (NTP, 1986b)] are also genotoxic chemicals. Rats are more susceptible than mice to the formation of oral cavity neoplasms, and oral cavity neoplasms have previously been reported only in the 1,2,3-trichloropropane mouse study (NTP, 1994c). Chemical-related esophageal neoplasms have previously been observed in rats in only two other studies [2,3-dibromo-1-propanol (NTP, 1994b) and dimethylvinyl chloride (NTP, 1986b)].

An increased incidence in benign and malignant neoplasms of the small and large intestine was seen in male rats. There was no increase in the incidence of intestinal neoplasms in female rats, but most of the neoplasms observed in males occurred in the stop-exposure group above the highest exposure level for females. In previous NTP studies where intestinal neoplasms have resulted from chemical administration, the number of neoplasms has been slightly greater in males than in females (bromoform; NTP, 1989a, bromodichloroethane; NTP, 1988a; 3,3-dimethylbenzidine; NTP, 1991b). Although the number of neoplasms in the small intestine were increased in the stop-exposure group, the response was much less than that observed for the large intestine. In previous NTP studies, a smaller number of neoplasms have been observed in the small intestine compared to the large intestine (3,3-dimethoxybenzidine; NCI, 1979a; dimethylhydrazine; Ward, 1974). In several instances there has been a marked increase in the incidence of neoplasms of the large intestine with no effect on the small intestine (bromoform, bromodichloromethane). In this study, most of the neoplasms of the large intestine were benign and were morphologically similar to the adenomas of the colon that rarely occur in controls. Six of the seven neoplasms of the small intestine were malignant and contained cystic areas as well as foci of osseous metaplasia. Morphologic features were similar to those that have been described for spontaneous and chemically induced neoplasms of the small intestine (Ward, 1974). Two gross lesions diagnosed as cystic hyperplasia and focal hyperplasia with osseous metaplasia in two other dosed rats are rare spontaneous lesions of the small intestine which may be preneoplastic. Other brominated chemicals also cause intestinal neoplasms in rats [bromodichloromethane (NTP, 1988a), tribromomethane (NTP, 1989a), 2,3-dibromo-1-propanol (NTP, 1994b), 1-amino-2,4-dibromoanthraquinone (NTP, 1996)], suggesting that these brominated chemicals may be acting by a similar mechanism.

There were increased incidences of urinary bladder transitional cell neoplasms in male rats at 15 months and 2 years. While these incidences were low, these neoplasms rarely occur in untreated animals (mean: 0.2%), and these neoplasms were considered to be related to treatment. Only 10 chemicals studied by the NTP have caused treatment-related urinary bladder neoplasms in male rats. It has been suggested that some of these chemicals caused the urinary bladder neoplasms by formation of calculi, subsequent irritation, and tumor formation (e.g., melamine; NTP, 1983), but this does not appear to be the mechanism for the development of urinary bladder neoplasms observed in the present study. The early occurrence of transitional cell hyperplasia suggests that 2,2-bis(bromomethyl)-1,3-propanediol or its metabolites have a direct toxic effect on the urinary bladder in male rats.

2,2-Bis(bromomethyl)-1,3-propanediol caused renal tubule degeneration and hyperplasia in male and female rats at 15 months and 2 years. Four renal tubule adenomas (one in the 5,000 ppm group and three in the 10,000 ppm group) occurred in male rats. These neoplasms are uncommon in males (mean: 2%) and may have been related to chemical administration. There was no evidence for a carcinogenic response in the kidney of the female rat.

2,2-Bis(bromomethyl)-1,3-propanediol exposure caused neoplasms of the thyroid gland in male and female rats. The occurrence of these neoplasms in the absence of diffuse thyroid gland hyperplasia supports the hypothesis that 2,2-bis(bromomethyl)-1,3-propanediol causes a direct thyroid response that is not likely secondary to sustained high concentrations of thyroid stimulating hormone.

There was a treatment-related increased incidence of mesothelioma in male rats. Mesothelioma typically

arises in the abdominal peritoneal cavity of F344 rats and is seen almost exclusively in males. Treatment-related increases of mesothelioma observed in previous NTP studies have also been in male rats. Other chemicals which have caused a marked increase in the incidence of mesotheliomas in male rats have also caused increases in mammary gland neoplasms in females (cytembena; NTP, 1981; glycidol; NTP, 1990b; *o*-toluidine; NCI, 1979b).

A marginal increase in the incidence of acinar cell adenoma of the pancreas was observed in exposed groups of male rats. Focal acinar cell hyperplasia was significantly increased in all exposure groups. Because there was no dose-related increase in the incidence of adenomas, and all incidences were within the NTP historical control range, it was uncertain if these neoplasms were related to treatment.

The stop-exposure study in male rats showed that 2,2-bis(bromomethyl)-1,3-propanediol administered for only 3 months was carcinogenic at all the sites where carcinogenic activity was observed in the 2-year continuous-exposure male rat study. The incidences of neoplasms were greater in the stop-exposure study male rats than in continuous-exposure male rats at the following sites: oral cavity, forestomach, small intestine, large intestine, lung, Zymbal's gland, thyroid gland, and mesothelium.

In the male stop-exposure group, there was an adenoma and a carcinoma of the seminal vesicle. The spontaneous development of these neoplasms is extremely rare in control rats, but treatment-related increases in hyperplasia and neoplasms have been reported in other strains of rats administered N-nitroso-N-methylurea (Slayter *et al.*, 1994) or 3,2'-dimethy-4-aminobiphenyl (Bosland *et al.*, 1990) followed by treatment with testosterone propionate or cyproterone acetate, respectively. Because of the rarity of these neoplasms in control rats and the presence of a dose-related increase in hyperplasia, the neoplasms in the stop-exposure group were considered to be related to treatment.

Based on the findings from this stop-exposure study, genetic damage appears to occur within the first few months of exposure. This genetic damage is irreversible, and neoplasms develop in the absence of a toxic response.

In a previous study of 2,2-bis(bromomethyl)-1,3-propanediol [(FR-1138®) containing approximately the same components of parent compound and impurities as used in these NTP studies], there were no clear carcinogenic effects in male or female Sprague-Dawley rats administered doses in the feed that were reported to deliver 5 or 100 mg/kg per day for 2 years (Keyes *et al.*, 1979).

In the NTP F344/N rat study, 2,2-bis(bromomethyl)-1,3-propanediol was administered at 2,500, 5,000, or 10,000 ppm, delivering approximately 100, 200, or 400 mg/kg of the chemical per day throughout most of the study. The low dose delivered in the present study was approximately the same as the higher dose in the Keyes *et al.* (1979) study, and at this dose, treatment-related neoplasms occurred in the subcutaneous tissues and oral cavity of male rats and mammary gland of female rats. As the dose was increased, a wider spectrum of carcinogenic responses occurred. The variance in the results for the two studies in rats may have been related to metabolic differences in the strains or differences in the incidence of spontaneous neoplasms in control animals. The Sprague-Dawley rat has a very high background incidence and multiplicity of mammary gland neoplasms, which could have masked this neoplastic effect of the chemical. In the male F344 rat, the small increase in the incidence of oral cavity neoplasms at the lowest dose (2,500 ppm) was significantly greater than the incidence in the control group, but the treatment-related increased incidences were more apparent at higher exposure levels than those used in the Keyes *et al.* (1979) study.

The incidences of harderian gland neoplasms were increased in exposed male and female mice. Other chemicals causing these neoplasms are usually multispecies/site carcinogens [benzene (NTP, 1986a), cupferron (NCI, 1978a), ethylene oxide (NTP, 1988b), glycidol (NTP, 1990b), *n*-methylolacryamide (NTP, 1989b), 4,4'oxydianiline (NCI, 1980), 1,2,3-trichloropropane (NTP, 1994c), and, 1,3-butadiene (NTP, 1993)].

The incidences of lung neoplasms were increased in exposed male and female mice. Lung neoplasms have been observed in mice (but not in rats) in studies of ozone (NTP, 1994d), benzene (NTP, 1986a), benzofuran (NTP, 1989c) as well as other

halogenated hydrocarbons [1,2-dibromo-3-chloropropane (NTP, 1982a), 1,2-dibromoethane (NCI, 1978b; NTP, 1982b), 2,3-dibromo-1-propanol (NTP, 1994b), 1,2-dichloroethane (NCI, 1978c), and tris(2,3-dibromopropyl)phosphate (NCI, 1978d)]. It is not known why the mouse lung is particularly responsive to the effects from these halogenated hydrocarbons, but this response could be due to differences in metabolism between species.

The toxicity observed in the urinary bladder and kidney of mice in the 13-week study was not seen in the 2-year study, but the highest dose (1,250 ppm) was below the level at which these lesions were seen in the 13-week study where there was renal toxicity characterized by papillary necrosis and increased tubule regeneration. Although the highest dose in the 2-year study was half the dose causing these lesions in the 13-week study, there was a small increase in the incidence of renal tubule adenoma in male mice. In NTP studies of approximately 450 chemicals, only seven other chemicals have been identified as causing kidney neoplasms in the male mouse. Two of these were brominated chemicals [bromodichloromethane (NTP, 1988a) and tris(2,3-dibromopropyl)phosphate (NCI, 1978d)].

Other neoplastic responses occurred in the forestomach of exposed male and female mice and the mammary gland and circulatory system in exposed female mice. Minimal increases in the incidences of neoplasms of the forestomach were seen in male and female mice. There was no treatment-related increase in the incidence of hyperplasia of the forestomach squamous epithelium. Because the number of forestomach neoplasms was within or just above the historical control range, it was uncertain if this increase was related to treatment.

In female mice, there was a significant increase in hemangiosarcoma and hemangioma (combined) in the 1,250 ppm group. Two of the hemangiosarcomas were in the subcutis, which was also a site for treatment-related sarcomas in female mice. Since the combined total number of neoplasms marginally exceeded the historical control range, it is uncertain if the increase in the incidence of these neoplasms was related to treatment.

Although 2,2-bis(bromomethyl)-1,3-propanediol caused mammary gland neoplasms in male and female rats, in exposed groups of female mice there were only four mammary gland carcinomas (one in the 625 ppm group and three in the 1,250 ppm group). Because the incidences for these neoplasms were within the historical range, it was uncertain if the increase was related to chemical administration.

2,2-Bis(bromomethyl)-1,3-propanediol and other brominated chemicals have been shown to be genotoxic in a spectrum of tests. It is hypothesized that the carcinogenic activity of brominated chemicals is due to genotoxic mechanisms, although at this time we have not identified the genotoxic metabolite or characterized the spectrum of genetic changes on a molecular level.

Of the 11 aliphatic and three aromatic brominated chemicals studied by the NTP in 2-year rodent studies, 13 of 14 chemicals were carcinogenic (Table 30). It would be expected that C-Br bonds in 2,2-bis(bromomethyl)-1,3-propanediol would be cleaved more readily than C-Cl bonds in halogenated compounds because of a lower bond energy (bond strengths: C-Cl, 95 kCal; C-Br, 67 kCal; Weast and Astle, 1978). Once the C-Br bond is broken, a free radical is available that can participate in various chemical reactions. Weiss *et al.* (1986) showed that eosinophils contain a lysosomal peroxidase that oxidizes halides to highly reactive and toxic hypohalous acids. Even though chloride is found at 1,000 times the concentration of bromide, the eosinophils used bromide preferentially to form the hypobromous acid. Bromide was shown to bind more readily to cellular proteins and macromolecules than other halide ions.

Two hypotheses for the carcinogenic activity of brominated chemicals are: 1) bromine causes oxidative damage to DNA and other cellular constituents and 2) the C-Br bond is broken and the remaining carbon-containing electrophilic group forms DNA adducts with subsequent DNA damage.

Studies with potassium bromate (Kurokawa *et al.*, 1983) have shown that this chemical administered in drinking water at 250 or 500 ppm to F344 rats caused renal and intestinal neoplasms in male and female rats and mesotheliomas of the peritoneum in

male rats. Following oral administration of $KBrO_3$ a significant increase of 8-hydroxydeoxyguanosine was observed in DNA. 8-Hydroxydeoxyguanosine is one of the DNA-damage products formed by oxygen radicals, and this is thought to be one of the DNA lesions involved in $KBrO_3$ carcinogenesis (Kasai *et al.* 1987; Sai *et al.*, 1992).

These NTP studies found that the flame retardant 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138®) was carcinogenic in rodents causing a wide spectrum of organ carcinogenic responses. Other brominated flame retardants have also been shown to be carcinogenic in rodents [2,3-dibromo-1-propanol, polybrominated biphenyl, tris (2,3-dibromopropyl)phosphate, and bis(2,3-dibromopropyl)-phosphate (Takada *et al.*, 1991; IARC, 1990)]. Of the 10 aliphatic and three aromatic brominated chemicals studied by the NTP in 2-year rodent studies, 12 were carcinogenic (Table 30).

Common sites for carcinogenic activity from the brominated chemicals studied by the NTP (Table 31) include oral cavity, forestomach, intestine, lung, and kidney. Treatment-related lesions are generally not seen at these sites early in the study, but develop with time. In the 2,2-bis(bromomethyl)-1,3-propanediol stop-exposure study, neoplasm development in the male rat requires only 3 months of exposure, and while lesions were not seen in the target organ at the end of this 3-month exposure period, the essential damage to the cell had been done, and carcinogenic lesions developed with time. Nonneoplastic lesions were observed in the pancreas, seminal vesicles, thyroid gland, lung, kidney, and urinary bladder in male rats; in the kidney of female rats; and in the lung of female mice. A carcinogenic response was observed in some of these organs; however, there were many sites where a carcinogenic response was observed in the absence of nonneoplastic lesions.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** of 2,2-bis-(bromomethyl)-1,3-propanediol (FR-1138®) in male F344/N rats based on increased incidences of neoplasms of the skin, subcutaneous tissue, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland, and seminal vesicle, and the increased incidence of mononuclear cell leukemia.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female F344/N rats based on increased incidences of neoplasms of the oral cavity, esophagus, mammary gland, and thyroid gland.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in male $B6C3F_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and kidney.

There was *clear evidence of carcinogenic activity* of 2,2-bis(bromomethyl)-1,3-propanediol in female $B6C3F_1$ mice based on increased incidences of neoplasms of the harderian gland, lung, and subcutaneous tissue.

Slight increases in the incidences of neoplasms of the pancreas and kidney in male rats; forestomach in male mice; and forestomach, mammary gland, and circulatory system in female mice may have also been related to treatment.

Exposure of male and female rats to 2,2-bis(bromomethyl)-1,3-propanediol was associated with alveolar/bronchiolar hyperplasia in the lung (males only); focal atrophy, papillary degeneration, transitional epithelial hyperplasia (pelvis), and papillary epithelial hyperplasia in the kidney; follicular cell hyperplasia in the thyroid gland (males only); hyperplasia in the seminal vesicle and pancreas (males only); mucosal hyperplasia in the forestomach (males only); and urinary bladder hyperplasia (males only). Exposure of mice to 2,2-bis(bromomethyl)-1,3-propanediol was associated with hyperplasia of the alveolar epithelium in females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

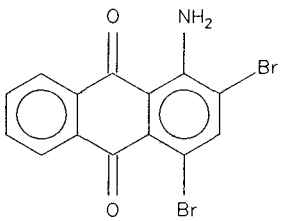
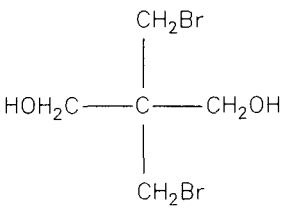
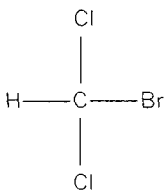
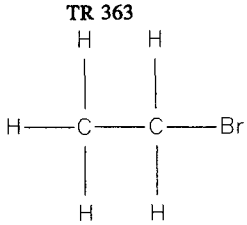
TABLE 29
Incidences of Selected Treatment-related Neoplasms in F344/N Rats and B6C3F$_1$ Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
Male Rats[a]	51	53	51	55	60
Skin Tumors (all types)[b]	4	6	14 **	24 **	21 **
Subcutaneous Tissue	2	9 *	13 **	16 **	10 **
Mammary Gland (fibroadenoma)	0	4 *	6 **	6 **	5 **
Zymbal's Gland	2	1	4	5	15 **
Oral Cavity	0	4 *	9 **	10 **	13 **
Esophagus	0	0	1	5 *	0
Forestomach	0	0	0	1	5 *
Small Intestine	0	0	0	2	5 *
Large Intestine	0	0	3	4	10 **
Mesothelioma	0	3	8 **	9 **	26 **
Kidney (renal tubule adenoma)	0	0	1	3 **	1
Urinary Bladder	0	0	1	3	2
Lung	1	1	3	4 *	7 *
Thyroid Gland, Follicular Cell	0	2	6 *	3	9 **
Seminal Vesicle	0	0	0	0	2
All Organs, Mononuclear Cell Leukemia	27	29	40 **	34 **	25 **
Pancreas	1	2	4 *	3	3
Female Rats	50	51	53	52	
Oral Cavity	2	3	5	6	
Esophagus	0	0	1	10 **	
Mammary Gland (fibroadenoma)	25	45 **	46 **	45 **	
Thyroid Gland, Follicular Cell	0	0	2	4 **	

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male Mice	50	51	50	49
Harderian Gland	4	7	16 **	22 **
Lung	15	11	16	25 *
Kidney	0	0	3	2
Forestomach	0	3	3	4 *
Female Mice	52	50	51	50
Harderian Gland	3	12 *	13 **	19 **
Lung	5	5	15 *	19 **
Subcutaneous Tissue	0	1	4	12 **
Forestomach	0	1	5 *	3 *
Mammary Gland	0	0	1	3
Circulatory System	1	2	0	5 *

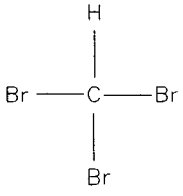
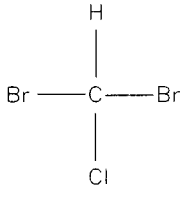
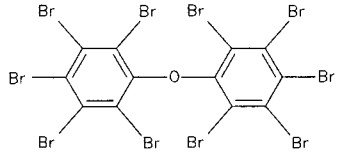
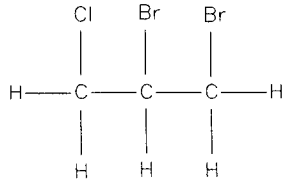
* Significantly different ($P \leq 0.05$) from controls by the life table test (Zymbal's gland or subcutaneous tissue neoplasms and mononuclear cell leukemia) or the logistic regression test (all other neoplasms)
** $P \leq 0.01$
[a] Number of animals necropsied
[b] Number of animals with neoplasms

TABLE 30
Results of Carcinogenicity and Mutagenicity Tests of Selected Brominated Chemicals in Male and Female F344/N Rats and Male and Female B6C3F$_1$ Mice[a]

Chemical and Route	Carcinogenicity[b] Male Rat	Female Rat	Male Mouse	Female Mouse	*Salmonella* Test Result
1-Amino-2,4-dibromoanthraquinone (feed) TR 383 (in press) 	+ L, I, K, Ub	+ L, I, K, Ub	+ L, F, Lu	+ L, F, Lu	+[c]
2,2-Bis(bromomethyl)-1,3-propanediol (feed) TR 452 	+ Sk, S, Oc, E, F, I, Ma, Lu, P, K, Ub, Sv, Z, Ty, Me	+ Oc, E, Ma, Lu, Ty, Z	+ F, Lu, K, Ha	+ S, F, Ma, Lu, H, Ci	+[d]
Bromodichloromethane (gavage) TR 321 	+ K, I	+ K	+ K	+ L	+[e]
Bromoethane (inhalation) TR 363 	+ A, Br, Lu	+/− Br, Lu	+/− Lu	+ U	+[f]

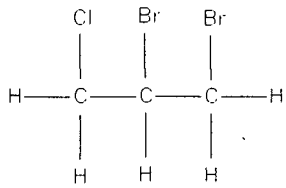
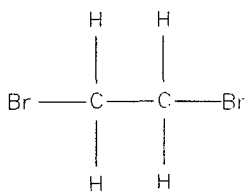
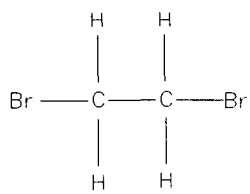
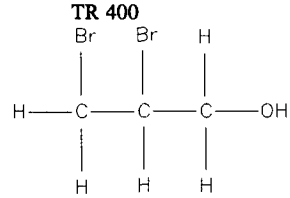
(continued)

TABLE 30
Results of Carcinogenicity and Mutagenicity Tests of Selected Brominated Chemicals in Male and Female F344/N Rats and Male and Female B6C3F$_1$ Mice (continued)

Chemical and Route	Carcinogenicity				*Salmonella* Test Result
	Male Rat	Female Rat	Male Mouse	Female Mouse	
Bromoform (tribromomethane; gavage) TR 350 	+ I	+ I	–	–	+[g]
Chlorodibromomethane (gavage) TR 282 	–	–	+/– L	+ L	+[e]
Decabromodiphenyl Oxide (feed) TR 309 	+ L	+ L	+/– L, Ty	–	–[c]
1,2-Dibromo-3-chloropropane (gavage) TR 28 	+ F	+ F, Ma	+ F	+ F	+[h]

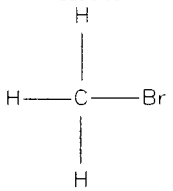
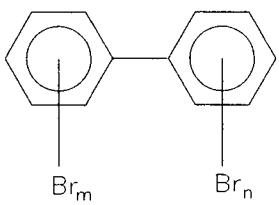
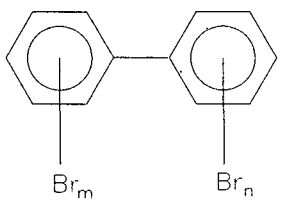
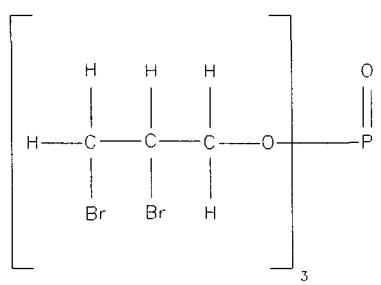
(continued)

TABLE 30
Results of Carcinogenicity and Mutagenicity Tests of Selected Brominated Chemicals in Male and Female F344/N Rats and Male and Female B6C3F$_1$ Mice (continued)

Chemical and Route	Carcinogenicity				*Salmonella* Test Result
	Male Rat	Female Rat	Male Mouse	Female Mouse	
1,2-Dibromo-3-chloropropane (inhalation) TR 206 	+ N, Oc	+ N, Oc, A	+ N, Lu	+ N, Lu	+[h]
1,2-Dibromoethane (gavage) TR 86 	+ F, Ci	+ F, L	+ F, Lu	+ F, Lu	+[i]
1,2-Dibromoethane (inhalation) TR 210 	+ N, Ci, Me	+ N, Ci, Ma, Lu	+ Lu	+ Lu, Ci, S, N, Ma	+[i]
2,3-Dibromo-1-propanol (dermal) TR 400 	+ N, Me, Sp, Sk, Oc, E, F, I, L, K, Z	+ Sk, Z, Cl, Ma, N, Oc, I, F, I, L, K	+ Sk, F, L, Lu	+ Sk, F	+[c]

(continued)

TABLE 30
Results of Carcinogenicity and Mutagenicity Tests of Selected Brominated Chemicals in Male and Female F344/N Rats and Male and Female B6C3F$_1$ Mice (continued)

Chemical and Route	Carcinogenicity				*Salmonella* Test Result
	Male Rat	Female Rat	Male Mouse	Female Mouse	
Methyl Bromide (inhalation) TR 385 	NT	NT	–	–	+[j]
Polybrominated Biphenyls[k] (gavage) TR 244 	+ L	+ L	+ L	+ L	NT
Polybrominated Biphenyls[k] (feed) TR 398 	+ L	+ L	+ L	+ L	NT
Tris (2,3-Dibromopropyl) Phosphate (feed) TR 76 	+ K	+ K, F, Lu	+ K, F, Lu	+ F, L, Lu	+[l]

(continued)

TABLE 30
Results of Carcinogenicity and Mutagenicity Tests of Selected Brominated Chemicals in Male and Female F344/N Rats and Male and Female B6C3F$_1$ Mice (continued)

[a] Carcinogenic response: + = some or clear evidence of carcinogenic activity; − = no evidence of carcinogenic activity; +/− = equivocal evidence of carcinogenic activity; NT = not tested
[b] Site of carcinogenic activity: A = adrenal gland; Br = brain; Ci = circulatory system; Cl = clitoral gland; E = esophagus; F = forestomach; H = harderian gland; He = hemangiosarcoma; I = intestine; K = kidney; L = liver; Lu = lung; Ma = mammary gland; Me = mesothelium; N = nasal cavity; Oc = oral cavity; P = pancreas; S = subcutaneous tissue; Sk = skin; Sp = spleen; Sv = seminal vesicle; Ty = thyroid gland; U = uterus; Ub = urinary bladder; and Z = Zymbal's gland
[c] Haworth *et al.*, 1983
[d] Mortelmans *et al.*, 1986; Zeiger *et al.*, 1992
[e] Simmon *et al.*, 1977; Simmon, 1978; Simmon and Kauhanen, 1978; Simmon and Tardiff, 1978
[f] Haworth *et al.*, 1983; Zeiger *et al.*, 1992
[g] Haworth *et al.*, 1983; Zeiger, 1990
[h] Zeiger *et al.*, 1988
[i] Zeiger *et al.*, 1992
[j] Unpublished
[k] Sum of m and n ranges from 2 to 7
[l] Dunkel *et al.*, 1985

TABLE 31
Summary of Selected Neoplasms in NTP Studies of Brominated Chemicals

	1-Amino-2,4-dibromoanthraquinone (feed)	2,2-Bis-(bromomethyl)-1,3-propanediol (feed)	Bromodichloromethane (gavage)	Bromoform (gavage)	Bromoethane (inhalation)
Alimentary System[a]					
Forestomach	MM, FM	MR	—	—	—
Intestine	MR, FR	MR	MR	MR, FR	—
Liver	MR, FR, MM, FM	—	FM	—	—
Oral Cavity	—	MR, FR	—	—	—
Circulatory System	—	—	—	—	—
Endocrine System					
Adrenal Gland	—	—	—	—	MR
Thyroid Gland	—	MR,FR	—	—	—
Hematopoietic System					
Spleen	—	—	—	—	—
Integumentary System					
Skin	—	MR	—	—	—
Mammary Gland	—	MR, FR	—	—	—
Mesothelium	—	MR	—	—	—
Nervous System					
Brain	—	—	—	—	MR, FR
Respiratory System					
Lung	MM, FM	MR	MR, FR, MM	—	MM
Nasal Cavity	—	—	—	—	—
Urinary System					
Kidney	MR, FR	MR	MR, FR, MM	—	—
Urinary Bladder	MR, FR	—	—	—	—
Other	—	MR, FR, MM, FM	—	—	FM

(continued)

TABLE 31
Summary of Selected Neoplasms in NTP Studies of Brominated Chemicals (continued)

	Chlorodibromomethane (gavage)	Decabromo-diphenyl Oxide (feed)	1,2-Dibromo-3-chloro-propane (gavage)	1,2-Dibromo-3-chloro-propane (inhalation)	1,2-Dibromoethane (gavage)
Alimentary System					
Forestomach	—	—	MR, FR, MM, FM	—	MR, FR, MM, FM
Intestine	—	—	—	—	—
Liver	MM, FM	MR, FR	—	—	FR
Oral Cavity	—	—	—	MR, FR	—
Circulatory System	—	—	—	—	MR
Endocrine System					
Adrenal Gland	—	—	—	—	—
Thyroid Gland	—	FM	—	—	—
Hematopoietic System					
Spleen	—	—	—	—	—
Integumentary System					
Skin	—	—	—	—	—
Mammary Gland	—	—	FR	—	—
Mesothelium	—	—	—	—	—
Nervous System					
Brain	—	—	—	—	—
Respiratory System					
Lung	—	—	—	MM, FM	MM, FM
Nasal Cavity	—	—	—	MR, FR, MM, FM	—
Urinary System					
Kidney	—	—	—	—	—
Urinary Bladder	—	—	—	—	—
Other	—	—	—	—	—

(continued)

TABLE 31
Summary of Selected Neoplasms in NTP Studies of Brominated Chemicals (continued)

	1,2-Dibromoethane (inhalation)	2,3-Dibromo-1-propanol (dermal)	Methyl Bromide[b] (inhalation)	Polybrominated Biphenyls (gavage/feed)	tris(2,3-Dibromopropyl) Phosphate (feed)
Alimentary System					
Forestomach	—	MR, FR, MM, FM	—	—	FR, MM, FM
Intestine	—	MR, FR	—	—	—
Liver	—	MR, FR, MM	—	MR, FR, MM, FM	FM
Oral Cavity	—	MR	—	—	—
Circulatory System	MR, FR, FM	—	—	—	—
Endocrine System					
Adrenal Gland	FR	—	—	—	—
Thyroid Gland	—	—	—	—	—
Hematopoietic System					
Spleen	MM	—	—	—	—
Integumentary System					
Skin	—	MR, MM, FM	—	—	—
Mammary Gland	FR, FM	FR	—	—	—
Mesothelium	MR	MR	—	—	—
Nervous System					
Brain	—	—	—	—	—
Respiratory System					
Lung	FR, MM, FM	MM	—	—	FR, MM, FM
Nasal Cavity	MR, FR, FM	MR, FR	—	—	—
Urinary System					
Kidney	—	MR, FR	—	—	MR, FR, MM
Urinary Bladder	—	—	—	—	—
Other	FM	MR, FR	—	—	—

[a] MR = male rats; FR = female rats; MM = male mice; FM = female mice
[b] Study conducted only in mice

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	70	60	60	60	70
3-Month interim evaluation[b]	10				10
15-Month interim evaluation	9	7	9	5	
Early deaths					
Moribund	24	30	36	43	55
Natural deaths	1	3	2	11	5
Survivors					
Terminal sacrifice	26	20	13	1	
Animals examined microscopically	70	60	60	60	70
Systems Examined at 3 Months With No Neoplasms Observed					
Alimentary System					
Cardiovascular System					
Endocrine System					
General Body System					
Genital System					
Hematopoetic System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Respiratory System					
Special Senses System					
Urinary System					
15-Month Interim Evaluation					
Alimentary System					
Liver	(9)	(7)	(9)	(5)	
Mesentery		(4)	(2)	(1)	
Endocrine System					
Adrenal cortex	(9)	(7)	(9)	(5)	
Adenoma		1 (14%)			
Adrenal medulla	(9)	(7)	(9)	(5)	
Pheochromocytoma benign	1 (11%)				
Islets, pancreatic	(9)	(7)	(9)	(5)	
Adenoma			1 (11%)		
Pituitary gland	(9)	(7)	(9)	(5)	
Pars distalis, adenoma	2 (22%)	1 (14%)			
Thyroid gland	(9)	(7)	(9)	(5)	
C-cell, adenoma		1 (14%)		1 (20%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Genital System					
Testes	(9)	(7)	(9)	(5)	
Bilateral, interstitial cell, adenoma	8 (89%)	6 (86%)	9 (100%)	4 (80%)	
Interstitial cell, adenoma				1 (20%)	
Integumentary System					
Skin	(9)	(7)	(9)	(5)	
Squamous cell papilloma		1 (14%)		1 (20%)	
Special Senses System					
Eye			(1)		
Lids, melanoma NOS			1 (100%)		
Urinary System					
Kidney	(9)	(7)	(9)	(5)	
Pelvis, transitional epithelium, carcinoma				1 (20%)	
Urinary bladder	(9)	(7)	(9)	(5)	
Transitional epithelium, papilloma				1 (20%)	
Systemic Lesions					
Multiple organs[c]	(9)	(7)	(9)	(5)	
Leukemia mononuclear	1 (11%)				
Mesothelioma malignant		1 (14%)	1 (11%)		
Systems Examined With No Neoplasms Observed					
Cardiovascular System					
General Body System					
Hematopoietic System					
Musculoskeletal System					
Nervous System					
Respiratory System					
2-Year Study					
Alimentary System					
Esophagus	(51)	(53)	(51)	(55)	(60)
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma			1 (2%)	5 (9%)	
Intestine large, colon	(51)	(52)	(51)	(54)	(59)
Carcinoma					1 (2%)
Carcinoma, multiple					1 (2%)
Hemangioma				1 (2%)	
Leiomyoma		1 (2%)			
Leiomyosarcoma			1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Intestine large, colon (continued)	(51)	(52)	(51)	(54)	(59)
Polyp adenomatous			3 (6%)	4 (7%)	8 (14%)
Polyp adenomatous, multiple					1 (2%)
Intestine large, rectum	(51)	(52)	(50)	(53)	(59)
Polyp adenomatous					1 (2%)
Intestine large, cecum	(51)	(52)	(51)	(54)	(59)
Intestine small, duodenum	(51)	(53)	(51)	(52)	(59)
Squamous cell carcinoma, metastatic, lung					1 (2%)
Intestine small, jejunum	(51)	(52)	(51)	(53)	(59)
Carcinoma				2 (4%)	2 (3%)
Polyp adenomatous					1 (2%)
Intestine small, ileum	(51)	(52)	(51)	(53)	(59)
Carcinoma					1 (2%)
Squamous cell carcinoma, metastatic, lung					1 (2%)
Mucosa, carcinoma					1 (2%)
Liver	(51)	(53)	(51)	(55)	(60)
Hepatocellular carcinoma					1 (2%)
Hepatocellular adenoma		1 (2%)			
Hepatocellular adenoma, multiple		1 (2%)			
Sarcoma				1 (2%)	
Sarcoma, metastatic, spleen				1 (2%)	
Mesentery	(15)	(16)	(19)	(22)	(30)
Carcinoma, metastatic, seminal vesicle					1 (3%)
Fibroma		1 (6%)			
Hemangiosarcoma			1 (5%)		
Sarcoma				2 (9%)	
Pancreas	(51)	(53)	(51)	(53)	(59)
Sarcoma				1 (2%)	
Squamous cell carcinoma, metastatic, lung					1 (2%)
Acinar cell, adenoma	1 (2%)	2 (4%)	4 (8%)	2 (4%)	2 (3%)
Acinar cell, adenoma, multiple				1 (2%)	1 (2%)
Pharynx		(3)	(4)	(5)	(10)
Palate, squamous cell carcinoma					2 (20%)
Palate, squamous cell papilloma		2 (67%)	3 (75%)	2 (40%)	7 (70%)
Salivary glands	(51)	(52)	(49)	(55)	(60)
Stomach, forestomach	(51)	(53)	(51)	(55)	(59)
Sarcoma				1 (2%)	
Squamous cell papilloma				1 (2%)	4 (7%)
Mucosa, squamous cell papilloma					1 (2%)
Stomach, glandular	(51)	(53)	(51)	(53)	(60)
Sarcoma				1 (2%)	
Tongue		(2)	(5)	(13)	(9)
Squamous cell papilloma		2 (100%)	5 (100%)	8 (62%)	5 (56%)
Squamous cell papilloma, multiple					1 (11%)
Tooth	(1)		(1)		(2)
Gingiva, squamous cell carcinoma			1 (100%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Cardiovascular System					
Heart	(51)	(53)	(51)	(55)	(60)
Carcinoma, metastatic, seminal vesicle					1 (2%)
Schwannoma NOS	1 (2%)	1 (2%)	1 (2%)		
Squamous cell carcinoma, metastatic, lung					1 (2%)
Endocrine System					
Adrenal cortex	(51)	(53)	(51)	(54)	(60)
Adenoma	1 (2%)		1 (2%)		
Squamous cell carcinoma, metastatic, lung					1 (2%)
Adrenal medulla	(51)	(53)	(51)	(54)	(60)
Pheochromocytoma malignant	3 (6%)	3 (6%)	1 (2%)	1 (2%)	
Pheochromocytoma complex				1 (2%)	
Pheochromocytoma benign	5 (10%)	9 (17%)	4 (8%)	4 (7%)	
Bilateral, pheochromocytoma benign	1 (2%)	3 (6%)			
Islets, pancreatic	(51)	(53)	(51)	(55)	(59)
Adenoma	1 (2%)	6 (11%)			
Carcinoma		2 (4%)	1 (2%)		
Parathyroid gland	(50)	(51)	(49)	(53)	(58)
Pituitary gland	(50)	(51)	(50)	(53)	(57)
Pars distalis, adenoma	7 (14%)	9 (18%)	6 (12%)	6 (11%)	5 (9%)
Pars distalis, carcinoma		1 (2%)			
Pars intermedia, adenoma	1 (2%)				1 (2%)
Thyroid gland	(51)	(53)	(51)	(55)	(59)
Bilateral, C-cell, carcinoma				1 (2%)	
C-cell, adenoma	7 (14%)	4 (8%)	4 (8%)	3 (5%)	4 (7%)
C-cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)	
Follicular cell, adenoma		1 (2%)	2 (4%)	2 (4%)	7 (12%)
Follicular cell, carcinoma		1 (2%)	4 (8%)	1 (2%)	2 (3%)
General Body System					
Tissue NOS	(1)	(2)	(3)	(6)	(8)
Pelvic, chordoma				1 (17%)	
Genital System					
Epididymis	(51)	(53)	(51)	(54)	(60)
Penis		(1)			
Sarcoma		1 (100%)			
Preputial gland	(51)	(52)	(51)	(55)	(60)
Adenoma	3 (6%)	3 (6%)	4 (8%)	4 (7%)	4 (7%)
Carcinoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)	
Duct, squamous cell papilloma	1 (2%)				
Prostate	(51)	(53)	(51)	(55)	(60)
Carcinoma, metastatic, seminal vesicle					1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Genital System (continued)					
Seminal vesicle	(51)	(53)	(51)	(55)	(60)
Adenoma					1 (2%)
Carcinoma					1 (2%)
Testes	(51)	(53)	(51)	(55)	(60)
Bilateral, interstitial cell, adenoma	44 (86%)	44 (83%)	47 (92%)	48 (87%)	52 (87%)
Interstitial cell, adenoma	5 (10%)	4 (8%)	4 (8%)	3 (5%)	7 (12%)
Hematopoietic System					
Bone marrow	(51)	(53)	(51)	(55)	(60)
Lymph node	(25)	(23)	(36)	(27)	(30)
Deep cervical, carcinoma, metastatic, thyroid gland			1 (3%)		
Lymph node, mandibular	(49)	(52)	(49)	(55)	(59)
Lymph node, mesenteric	(50)	(53)	(51)	(55)	(60)
Spleen	(51)	(53)	(51)	(54)	(60)
Carcinoma, metastatic, seminal vesicle					1 (2%)
Fibroma				1 (2%)	
Sarcoma	1 (2%)			1 (2%)	
Thymus	(49)	(53)	(49)	(53)	(57)
Epithelial cell, thymoma malignant				1 (2%)	
Epithelial cell, thymoma NOS					1 (2%)
Integumentary System					
Mammary gland	(48)	(51)	(49)	(48)	(50)
Adenoma			1 (2%)	1 (2%)	
Fibroadenoma		3 (6%)	4 (8%)	6 (13%)	4 (8%)
Fibroadenoma, multiple		1 (2%)	2 (4%)		1 (2%)
Skin	(51)	(53)	(51)	(54)	(59)
Basal cell adenoma		1 (2%)		3 (6%)	6 (10%)
Basal cell carcinoma			2 (4%)	2 (4%)	
Carcinoma, metastatic, Zymbal's gland				1 (2%)	
Keratoacanthoma	2 (4%)	5 (9%)	9 (18%)	16 (30%)	9 (15%)
Keratoacanthoma, multiple	1 (2%)		2 (4%)		1 (2%)
Squamous cell carcinoma					1 (2%)
Squamous cell papilloma	1 (2%)		2 (4%)	4 (7%)	10 (17%)
Squamous cell papilloma, multiple				1 (2%)	1 (2%)
Trichoepithelioma				1 (2%)	1 (2%)
Pinna, melanoma malignant		1 (2%)			
Sebaceous gland, adenoma		1 (2%)		2 (4%)	2 (3%)
Subcutaneous tissue, carcinoma, metastatic, thyroid gland			1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	8 (15%)	7 (14%)	9 (17%)	7 (12%)
Subcutaneous tissue, fibroma, multiple			4 (8%)	6 (11%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)			1 (2%)
Subcutaneous tissue, hemangiosarcoma				1 (2%)	
Subcutaneous tissue, lipoma			1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Integumentary System (continued)					
Skin (continued)	(51)	(53)	(51)	(54)	(59)
Subcutaneous tissue, sarcoma			2 (4%)	2 (4%)	2 (3%)
Subcutaneous tissue, sarcoma, multiple				1 (2%)	
Subcutaneous tissue, schwannoma malignant		2 (4%)			
Musculoskeletal System					
Bone	(51)	(53)	(51)	(55)	(60)
Osteosarcoma	1 (2%)				
Skeletal muscle		(3)	(2)	(4)	(4)
Hemangiosarcoma					1 (25%)
Squamous cell carcinoma, metastatic, lung					1 (25%)
Thymoma malignant, metastatic				1 (25%)	
Nervous System					
Brain	(51)	(53)	(51)	(55)	(60)
Astrocytoma NOS			1 (2%)		
Carcinoma, metastatic, pituitary gland		1 (2%)			
Oligodendroglioma NOS		1 (2%)			
Squamous cell carcinoma, metastatic, lung					1 (2%)
Respiratory System					
Lung	(51)	(53)	(51)	(55)	(60)
Alveolar/bronchiolar adenoma	1 (2%)		3 (6%)	1 (2%)	4 (7%)
Alveolar/bronchiolar carcinoma		1 (2%)		2 (4%)	2 (3%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)	1 (2%)
Carcinoma, multiple, metastatic, seminal vesicle					1 (2%)
Carcinoma, multiple, metastatic, thyroid gland				1 (2%)	
Carcinoma, multiple, metastatic, Zymbal's gland	1 (2%)				
Carcinoma, metastatic, Zymbal's gland				2 (4%)	1 (2%)
Chordoma, metastatic, tissue NOS				1 (2%)	
Sarcoma				1 (2%)	
Sarcoma, metastatic, tissue NOS		1 (2%)			
Squamous cell carcinoma					3 (5%)
Thymoma malignant, metastatic, thymus				1 (2%)	
Nose	(51)	(53)	(51)	(55)	(60)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Special Senses System					
Eye	(2)	(1)	(2)		(1)
Lids, melanoma NOS	1 (50%)				
Zymbal's gland	(2)	(1)	(5)	(5)	(15)
Adenoma			1 (20%)	3 (60%)	2 (13%)
Carcinoma	2 (100%)	1 (100%)	3 (60%)	2 (40%)	13 (87%)
Bilateral, carcinoma					2 (13%)
Urinary System					
Kidney	(51)	(53)	(51)	(55)	(59)
Squamous cell carcinoma, metastatic, lung					1 (2%)
Pelvis, transitional epithelium, carcinoma					1 (2%)
Renal tubule, adenoma			1 (2%)	3 (5%)	1 (2%)
Urinary bladder	(51)	(53)	(51)	(55)	(59)
Transitional epithelium, carcinoma				1 (2%)	1 (2%)
Transitional epithelium, papilloma			1 (2%)	2 (4%)	1 (2%)
Systemic Lesions					
Multiple organs	(51)	(53)	(51)	(55)	(60)
Leukemia mononuclear	27 (53%)	29 (55%)	40 (78%)	34 (62%)	25 (42%)
Mesothelioma malignant		3 (6%)	8 (16%)	9 (16%)	26 (43%)
Neoplasm Summary					
Total animals with primary neoplasms[d]					
15-Month interim evaluation	9	7	9	5	
2-Year study	51	52	51	54	60
Total primary neoplasms					
15-Month interim evaluation	12	11	12	9	
2-Year study	123	162	195	228	255
Total animals with benign neoplasms					
15-Month interim evaluation	9	7	9	5	
2-Year study	50	52	51	54	59
Total benign neoplasms					
15-Month interim evaluation	11	10	10	8	
2-Year study	84	112	127	153	163
Total animals with malignant neoplasms					
15-Month interim evaluation	1	1	1	1	
2-Year study	32	35	46	49	55
Total malignant neoplasms					
15-Month interim evaluation	1	1	1	1	
2-Year study	37	48	66	75	91
Total animals with metastatic neoplasms					
15-Month interim evaluation					
2-Year study	1	3	1	6	4
Total metastatic neoplasms					
15-Month interim evaluation					
2-Year study	1	4	2	8	16

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
Neoplasm Summary (continued)					
Total animals with uncertain neoplasms - benign or malignant					
15-Month interim evaluation			1		
2-Year study	2	2	2		1
Total uncertain neoplasms					
15-Month interim evaluation			1		
2-Year study	2	2	2		1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Ten control and ten 20,000 ppm (stop-exposure) rats were evaluated at 3 months.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm

Number of Days on Study	3 3 4	4 6 7	4 8 1	5 1 9	6 0 8	6 1 9	6 1 9	6 2 8	6 2 9	6 3 1	6 5 9	6 6 0	6 6 3	6 7 5	6 7 5	6 7 5	6 8 2	6 9 6	6 9 7	7 0 3	7 1 6	7 2 1	7 2 2	7 2 5	7 2 6
Carcass ID Number	0 1 0	0 1 7	0 2 1	0 3 7	0 0 7	0 0 3	0 0 5	0 3 3	0 2 4	0 4 5	0 4 2	0 3 5	0 2 2	0 0 2	0 0 4	0 4 3	0 1 6	0 0 1	0 2 0	0 3 0	0 2 3	0 2 6	0 1 5	0 3 6	0 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+		+						+	+			+	+	+	+		+			+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel		+	+	+																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																								X	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																								X	
Pheochromocytoma benign								X															X		
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X		X					X		X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X									X									
C-cell, carcinoma																							X		
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 8	0 3 9	0 4 0	0 4 1	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	0 5 1	0 0 6	0 0 8	0 0 9	0 1 1	0 1 2	0 1 3	0 1 4	0 1 8	0 1 9	0 2 7	0 2 8	0 2 9	0 3 1	0 3 2	0 3 4	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery													+				+			+						+	15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell, adenoma		X																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth																						+					1
Cardiovascular System																											
Blood vessel																											3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Schwannoma NOS																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma							X																				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant										X			X														3
Pheochromocytoma benign	X		X																				X				5
Bilateral, pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																					X						1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X						X																			X	7
Pars intermedia, adenoma																					X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma	X			X									X	X	X												7
C-cell, carcinoma																											1
General Body System																											
Tissue NOS																										+	1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	3	4	4	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	3	6	8	1	0	1	1	2	2	3	5	6	6	7	7	7	8	9	9	0	1	2	2	2
	4	7	1	9	8	9	9	8	9	1	9	0	3	5	5	5	2	6	7	3	6	1	2	5	6
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	2	3	0	0	0	3	2	4	4	3	2	0	0	4	1	0	2	3	2	2	1	3	2
	0	7	1	7	7	3	5	3	4	5	2	5	2	2	4	3	6	1	0	0	3	6	5	6	5
Genital System (continued)																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma								X											X						
Duct, squamous cell papilloma													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X	X	X		X	X	X		X			X	X	X	X	X	X	X
Interstitial cell, adenoma											X				X			X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+	+	+	+	+	+	+		+	+	+	+			+	+	+	+	+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal		+	+		+	+	+	+	+	+	+		+	+	+	+				+	+	+	+		+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma						X																			
Keratoacanthoma, multiple																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Carcinoma, multiple, metastatic, Zymbal's gland							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	
Lids, melanoma NOS																									
Zymbal's gland	+						+																		
Carcinoma	X						X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 8	0 3 9	0 4 0	0 4 1	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	0 5 1	0 5 6	0 0 8	0 0 9	0 1 1	0 1 2	0 1 3	0 1 4	0 1 8	0 1 9	0 2 7	0 2 8	0 2 9	0 3 1	0 3 2	0 3 3	Total Tissues/ Tumors
Genital System (continued)																											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma					X	X							X														3
Carcinoma																											2
Duct, squamous cell papilloma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma			X							X																	5
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node						+							+		+	+									+	+	25
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal																+									+	+	21
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																											
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Keratoacanthoma	X																										2
Keratoacanthoma, multiple																					X						1
Squamous cell papilloma																		X									1
Subcutaneous tissue, fibroma																									X		2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Osteosarcoma																							X				1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma																											1
Carcinoma, multiple, metastatic, Zymbal's gland																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye																					+						2
Lids, melanoma NOS																					X						1
Zymbal's gland																											2
Carcinoma																											2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	3	4	4	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	
	3	6	8	1	0	1	1	2	2	3	5	6	6	7	7	7	8	9	9	0	1	2	2	2	
	4	7	1	9	8	9	9	8	9	1	9	0	3	5	5	5	2	6	7	3	6	1	2	5	6
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	2	3	0	0	0	3	2	4	4	3	2	0	0	4	1	0	2	3	2	2	1	3	2
	0	7	1	7	7	3	5	3	4	5	2	5	2	2	4	3	6	1	0	0	3	6	5	6	5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X	X	X			X	X	X		X	X	X	X		X		X	X	X	X	X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 3 8	0 3 9	0 4 0	0 4 1	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	0 5 1	0 0 6	0 0 8	0 0 9	0 1 1	0 1 2	0 1 3	0 1 4	0 1 8	0 1 9	0 2 7	0 2 8	0 2 9	0 3 1	0 3 2	0 3 4	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear		X								X			X		X	X				X	X					X	27

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm

Number of Days on Study	2 3 5	4 5 0	4 5 1	4 6 7	4 8 0	5 1 2	5 1 2	5 3 7	5 4 3	5 4 8	5 5 5	5 6 8	5 7 6	5 8 6	5 8 6	6 1 0	6 2 0	6 4 5	6 4 8	6 5 9	6 6 0	6 6 2	6 7 5	6 7 5	6 8 1	6 8 1
Carcass ID Number	0 8 6	0 7 3	0 8 8	1 0 5	0 9 4	0 8 5	1 1 5	1 2 2	0 8 4	0 9 6	0 1 3	1 0 9	0 7 6	1 1 6	0 8 9	1 0 1	0 9 9	1 9 4	0 1 5	1 9 2	0 0 7	0 9 3	1 1 1	0 7 8	1 0 8	1 8 7	1 1 8
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma		X																									
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																											
Hepatocellular adenoma, multiple																											
Mesentery		+			+		+	+		+					+	+	+	+	+	+	+		+		+		
Fibroma		X																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																											
Pharynx																											
Palate, squamous cell papilloma																											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																											
Squamous cell papilloma																											
Cardiovascular System																											
Blood vessel								+																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																											X
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																											
Pheochromocytoma benign									X											X					X		
Bilateral, pheochromocytoma benign																			X				X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X								
Carcinoma									X																		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X																X			X		
Pars distalis, carcinoma																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																											
C-cell, carcinoma																											
Follicular cell, adenoma																											
Follicular cell, carcinoma																X											
General Body System																											
Tissue NOS														+	+												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	7 1 1	7 1 6	7 2 3	7 2 5	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 7 1	0 8 0	0 8 2	0 7 5	1 1 9	0 9 7	1 1 7	0 7 2	0 7 4	0 7 6	0 7 7	0 8 1	0 8 3	0 9 0	0 9 1	0 9 2	0 9 8	1 0 0	1 0 4	1 0 6	1 0 9	1 1 0	1 1 2	1 1 3	1 2 0	1 2 1	1 2 3	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leiomyoma																												1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular adenoma																										X		1
Hepatocellular adenoma, multiple									X																			1
Mesentery			+			+																						16
Fibroma																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Acinar cell, adenoma												X												X				2
Pharynx									+												+					+		3
Palate, squamous cell papilloma									X												X							2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue		I						+																	+			2
Squamous cell papilloma								X																	X			2
Cardiovascular System																												
Blood vessel																												1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Schwannoma NOS																												1
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant						X			X												X							3
Pheochromocytoma benign				X					X										X	X		X					X	9
Bilateral, pheochromocytoma benign																X												3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma						X					X	X											X		X			6
Carcinoma					X																							2
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma				X									X			X	X			X				X				9
Pars distalis, carcinoma																							X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma			X							X				X			X											4
C-cell, carcinoma			X																									1
Follicular cell, adenoma											X																	1
Follicular cell, carcinoma																												1
General Body System																												
Tissue NOS																												2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	2	4	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	3	5	5	6	8	1	1	3	4	4	5	6	7	8	8	1	2	4	4	5	6	6	7	7	8	8
	5	0	1	7	0	2	2	7	3	8	5	8	6	6	6	0	0	5	8	9	0	2	5	5	1	1
Carcass ID Number	0	0	0	1	0	0	1	1	0	0	1	0	1	0	1	0	1	0	1	1	0	1	0	1	0	1
	8	7	8	0	9	8	1	2	8	9	0	7	1	8	0	9	1	9	0	0	9	1	7	0	8	1
	6	3	8	5	4	5	5	2	4	6	3	9	6	9	1	9	4	5	2	7	3	1	8	8	7	8
Genital System																										
Coagulating gland																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																										
Sarcoma																										
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X							
Carcinoma																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Interstitial cell, adenoma						X																				
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+		+	+	+	+	+				+	+	+	+	+	+			+			
Mediastinal, mesothelioma malignant, metastatic, mesentery																		X								
Lymph node, bronchial							+																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal					+		+	+	+	+	+				+	+										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																		X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																										
Fibroadenoma, multiple																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																				X						
Keratoacanthoma																										
Pinna, melanoma malignant																		X								
Sebaceous gland, adenoma																										
Subcutaneous tissue, fibroma													X	X				X					X	X		
Subcutaneous tissue, fibrosarcoma																										
Subcutaneous tissue, schwannoma malignant																										X
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+								
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																										
Oligodendroglioma NOS											X															
Spinal cord				+				+																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	7 1 1	7 1 6	7 2 3	7 2 5	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 7 1	0 8 0	0 8 2	0 7 5	1 1 9	0 9 7	1 1 7	0 7 2	0 7 4	0 7 6	0 7 7	0 8 1	0 8 3	0 9 0	0 9 1	0 9 2	0 9 8	0 0 0	1 0 4	1 0 6	1 0 9	1 1 0	1 1 2	1 1 3	1 2 0	1 2 1	1 2 3	Total Tissues/ Tumors
Genital System																											
Coagulating gland																						+					1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Penis																									+		1
Sarcoma																									X		1
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma				X																		X					3
Carcinoma								X																			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, interstitial cell, adenoma	X	X			X	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X	44
Interstitial cell, adenoma			X	X							X																4
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node			+	+		+		+	+	+	+			+						+					+		23
Mediastinal, mesothelioma malignant, metastatic, mesentery																											1
Lymph node, bronchial																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal									+	+	+			+													12
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesothelioma malignant, metastatic, mesentery																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Integumentary System																											
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroadenoma						X			X									X									3
Fibroadenoma, multiple																									X		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Basal cell adenoma																											1
Keratoacanthoma						X					X		X			X									X		5
Pinna, melanoma malignant																											1
Sebaceous gland, adenoma								X																			1
Subcutaneous tissue, fibroma										X											X		X				8
Subcutaneous tissue, fibrosarcoma																	X										1
Subcutaneous tissue, schwannoma malignant														X													2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle							+						+														3
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, pituitary gland																							X				1
Oligodendroglioma NOS																											1
Spinal cord																				+					+		4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	2 3 5	4 5 0	4 5 1	4 6 7	4 8 0	5 1 2	5 1 2	5 3 7	5 4 3	5 4 8	5 5 5	5 6 8	5 7 6	5 8 6	5 8 6	6 1 0	6 2 0	6 4 5	6 4 8	6 5 9	6 6 0	6 6 2	6 7 5	6 7 5	6 8 1	6 8 1
Carcass ID Number	0 8 6	0 7 3	0 8 8	1 0 5	0 9 4	0 8 5	1 1 5	1 2 2	0 8 4	0 9 6	1 0 3	0 7 9	1 1 6	0 8 9	1 0 1	0 9 1	1 1 9	0 9 4	1 9 5	1 0 2	1 0 7	1 9 3	0 1 1	1 7 8	0 1 8	1 8 7	1 1 8
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																											
Sarcoma, metastatic, tissue NOS		X																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																											
Ear								+											+								
Eye																											
Zymbal's gland																											
Carcinoma																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X	X		X		X			X	X	X		X	X	X		X		X		
Mesothelioma malignant															X	X		X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	6 9 5	6 9 6	7 1 1	7 1 6	7 2 3	7 2 5	7 2 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 7 1	0 8 0	0 8 2	0 7 5	1 1 9	0 9 7	1 1 7	0 7 2	0 7 4	0 7 6	0 7 7	0 8 1	0 8 3	0 9 0	0 9 1	0 9 2	0 9 8	1 0 0	1 0 4	1 0 6	1 0 9	1 1 0	1 1 2	1 1 3	1 2 0	1 2 1	1 2 3	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar carcinoma																		X									1
Sarcoma, metastatic, tissue NOS																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																											
Ear																											2
Eye																		+									1
Zymbal's gland		+																									1
Carcinoma		X																									1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urethra																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X		X			X	X	X	X	X	X			X	X		X	X	X		X		X		X		29
Mesothelioma malignant																											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm

Number of Days on Study	4 5 1	5 3 6	5 3 6	5 6 4	5 7 6	5 9 2	6 0 5	6 0 8	6 0 8	6 0 0	6 2 1	6 2 1	6 2 7	6 2 3	6 3 3	6 4 1	6 4 1	6 4 1	6 4 5	6 5 4	6 5 6	6 6 2	6 6 6	6 6 3	6 7 3	6 8 1
Carcass ID Number	1 8 0	1 7 1	1 7 4	1 8 1	1 5 4	1 6 7	1 7 7	1 5 2	1 7 5	1 4 9	1 3 1	1 7 6	1 7 3	1 3 7	1 3 3	1 3 5	1 4 6	1 7 2	1 6 8	1 6 4	1 5 7	1 4 2	1 5 0	1 6 1	1 4 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+			+	+											+					+				+
Hemangiosarcoma	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Pharynx																	+								+
Palate, squamous cell papilloma																	X								X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue		+																							
Squamous cell papilloma		X																							
Tooth																									
Gingiva, squamous cell carcinoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																	X								
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X						X		
C-cell, carcinoma																					X				
Follicular cell, adenoma																						X			
Follicular cell, carcinoma														X											
General Body System																									
Tissue NOS																	+								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 4	6 8 9	6 9 4	6 9 5	6 9 6	6 9 6	6 9 7	6 9 7	7 0 3	7 2 2	7 2 6	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 4 3	1 6 3	1 5 5	1 5 1	1 6 5	1 4 0	1 5 9	1 5 8	1 6 0	1 3 6	1 5 6	1 3 2	1 5 3	1 3 4	1 3 8	1 3 9	1 4 1	1 4 4	1 4 7	1 4 8	1 6 2	1 6 6	1 6 9	1 7 0	1 7 8	1 7 9	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leiomyosarcoma	X																										1
Polyp adenomatous	X				X											X											3
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery	+	+	+		+	+			+	+		+	+					+	+					+		+	19
Hemangiosarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinar cell, adenoma																X		X				X	X				4
Pharynx					+																	+					4
Palate, squamous cell papilloma																						X					3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue				+			+														+					+	5
Squamous cell papilloma				X			X														X					X	5
Tooth									+																		1
Gingiva, squamous cell carcinoma									X																		1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Schwannoma NOS																								X			1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant																											1
Pheochromocytoma benign				X			X																		X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma																											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X				X									X			X	X								6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma														X										X			4
C-cell, carcinoma																											1
Follicular cell, adenoma								X																			2
Follicular cell, carcinoma	X																					X			X		4
General Body System																											
Tissue NOS	+								+																		3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	4 5 1	5 3 6	5 3 6	5 6 4	5 7 6	5 9 2	6 0 5	6 0 8	6 0 8	6 2 0	6 2 1	6 2 1	6 2 7	6 3 3	6 4 1	6 4 1	6 4 1	6 4 5	6 5 4	6 5 6	6 6 2	6 6 6	6 6 3	6 7 1	6 8 1
Carcass ID Number	1 1 8 0	1 7 1	1 7 4	1 8 1	1 5 4	1 6 7	1 7 7	1 5 2	1 7 5	1 4 9	1 3 1	1 7 6	1 7 3	1 3 7	1 3 3	1 3 5	1 4 6	1 7 2	1 6 8	1 6 4	1 5 7	1 4 2	1 5 0	1 6 1	1 4 5
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X			X												
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Interstitial cell, adenoma					X														X						X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+	+	+		+	+			+	+	+	+	+	+	+	+		+	+
Deep cervical, carcinoma, metastatic, thyroid gland																					X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+			+			+	+			+	+			+	+	+					+		+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																									
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma														X				X		X		X			
Keratoacanthoma, multiple																	X								
Squamous cell papilloma																			X						
Subcutaneous tissue, carcinoma, metastatic, thyroid gland																				X					
Subcutaneous tissue, fibroma			X									X			X				X	X					
Subcutaneous tissue, fibroma, multiple													X				X							X	
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS										X															
Spinal cord																		+							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 4	6 8 9	6 9 4	6 9 5	6 9 6	6 9 6	6 9 7	6 9 7	7 0 3	7 2 2	7 2 6	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 4 3	1 6 3	1 5 5	1 5 1	1 6 5	1 4 0	1 5 9	1 5 8	1 6 0	1 3 6	1 5 6	1 3 2	1 5 3	1 3 4	1 3 8	1 3 9	1 4 1	1 4 4	1 4 7	1 4 8	1 6 2	1 6 6	1 6 9	1 7 0	1 7 8	1 7 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																		X						X		4
Carcinoma					X																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Interstitial cell, adenoma			X																							4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+		+	+	+			+	+	+	+		+			+	+	+	+	+		+	+	36
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mediastinal	+	+	+			+	+			+	+	+	+		+			+		+	+					25
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma		X																								1
Fibroadenoma												X				X								X		4
Fibroadenoma, multiple															X							X				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Basal cell carcinoma				X	X																					2
Keratoacanthoma				X		X							X												X	9
Keratoacanthoma, multiple			X																							2
Squamous cell papilloma																				X						2
Subcutaneous tissue, carcinoma, metastatic, thyroid gland																										1
Subcutaneous tissue, fibroma								X																X		7
Subcutaneous tissue, fibroma, multiple													X													4
Subcutaneous tissue, lipoma																						X				1
Subcutaneous tissue, sarcoma		X																								2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle									+			+														2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Astrocytoma NOS																										1
Spinal cord																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	4 5 1	5 3 6	5 3 6	5 6 4	5 7 6	5 9 2	6 0 5	6 0 8	6 0 8	6 2 0	6 2 1	6 2 1	6 2 7	6 3 3	6 4 1	6 4 1	6 4 1	6 4 5	6 5 4	6 5 6	6 6 2	6 6 6	6 7 3	6 8 1
Carcass ID Number	1 8 0	1 7 1	1 7 4	1 8 1	1 5 4	1 6 7	1 7 7	1 5 2	1 7 5	1 4 9	1 3 1	1 7 6	1 7 3	1 3 7	1 3 3	1 3 5	1 4 6	1 7 2	1 6 8	1 6 4	1 5 7	1 4 2	1 5 0	1 6 1	1 4 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+																				
Zymbal's gland						+		+										+		+					
Adenoma																									
Carcinoma						X		X										X							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X			X	X	X	X	X	X			X	X	X	X	X	X	X	X		X	X
Mesothelioma malignant																									X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 4	6 8 9	6 9 4	6 9 5	6 9 6	6 9 6	6 9 7	6 9 7	7 0 3	7 2 2	7 2 6	7 3 1	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 9	
Carcass ID Number	1 4 3	1 6 3	1 5 5	1 5 1	1 6 5	1 4 0	1 5 9	1 5 8	1 6 0	1 3 6	1 5 6	1 3 2	1 5 3	1 3 4	1 3 8	1 3 9	1 4 1	1 4 4	1 4 7	1 4 8	1 6 2	1 6 6	1 6 9	1 7 0	1 7 8	1 7 9	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma	X																		X						X		3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye		+																									2
Zymbal's gland				+																							5
Adenoma				X																							1
Carcinoma																											3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, adenoma					X																						1
Urethra										+																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Transitional epithelium, papilloma																	X										1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X	X	X			X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	40
Mesothelioma malignant	X								X			X						X	X					X		X	8

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm

Number of Days on Study	1 4 9	3 8 1	3 9 3	4 3 2	4 5 1	4 7 1	4 9 5	5 0 9	5 1 3	5 1 6	5 2 3	5 4 1	5 4 2	5 4 4	5 4 9	5 5 6	5 6 7	5 6 7	5 6 7	5 7 8	5 7 0	5 7 0	5 7 4	5 7 6	5 7 6
Carcass ID Number	2 4 7	2 0 9	1 9 2	2 3 8	2 0 0	2 1 4	1 9 4	2 0 8	2 2 3	2 0 3	2 0 6	2 0 4	2 0 4	2 2 4	2 1 6	2 3 3	2 3 6	2 2 2	2 3 8	1 9 5	2 1 5	2 4 2	2 2 6	2 1 1	2 3 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma															X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Polyp adenomatous								X																	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																X									
Sarcoma, metastatic, spleen																									
Mesentery						+	+	+	+		+					+	+	+		+				+	
Sarcoma						X										X									
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																X									
Acinar cell, adenoma																									
Acinar cell, adenoma, multiple																									
Pharynx								+																	
Palate, squamous cell papilloma								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																X									
Squamous cell papilloma																									
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																X									
Tongue		+				+		+						+		+			+		+	+			
Squamous cell papilloma		X														X						X			
Cardiovascular System																									
Blood vessel															+										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									
Pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	5 7 7	5 8 5	5 8 6	5 9 8	6 0 4	6 0 8	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 0	6 4 3	6 4 7	6 5 4	6 5 8	6 6 2	6 6 2	6 7 0	6 8 1	6 8 2	6 8 7	6 9 0	6 9 5	6 9 7	7 0 9	7 1 1	7 2 3	7 3 3	7 3 6	
Carcass ID Number	2 2 9	2 3 4	2 4 1	2 2 1	2 3 2	2 4 3	2 3 1	2 0 7	2 1 7	2 2 0	2 1 2	2 4 4	1 9 1	2 3 0	2 1 0	1 9 7	2 0 2	2 2 7	2 0 1	2 4 0	1 9 8	1 9 6	1 9 9	2 1 8	2 0 5	2 2 5	2 9 3	1 1 9	2 1 3	2 2 3	2 3 9	Total Tissues/ Tumors
Alimentary System																															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Squamous cell carcinoma																				X											1
Squamous cell papilloma				X					X																X				X		5
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Hemangioma																													X		1
Polyp adenomatous		X																						X			X				4
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma									X										X												2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Sarcoma																															1
Sarcoma, metastatic, spleen																														X	1
Mesentery					+		+	+				+			+				+	+			+		+			+	+	+	22
Sarcoma																															2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma																															1
Acinar cell, adenoma					X																			X							2
Acinar cell, adenoma, multiple																										X					1
Pharynx												+												+	+		+				5
Palate, squamous cell papilloma																									X						2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Sarcoma																															1
Squamous cell papilloma					X																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma																															1
Tongue			+						+		+		+									+									13
Squamous cell papilloma			X						X		X		X									X									8
Cardiovascular System																															
Blood vessel																														+	2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Endocrine System																															
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	54
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	54
Pheochromocytoma malignant	X																														1
Pheochromocytoma complex			X																												1
Pheochromocytoma benign	X					X														X											4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma					X								X		X								X			X			X		6

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	1 4 9	3 8 1	3 9 3	4 3 2	4 5 1	4 7 1	4 9 5	5 0 9	5 1 3	5 1 6	5 2 3	5 4 1	5 4 2	5 4 4	5 4 9	5 5 6	5 6 7	5 6 7	5 6 7	5 7 8	5 7 0	5 7 0	5 7 4	5 7 6	5 7 6
Carcass ID Number	2 4 7	2 0 9	1 9 2	2 3 8	2 0 0	2 1 4	1 9 4	2 0 8	2 2 3	2 0 3	2 0 6	2 0 4	2 2 4	2 1 6	2 3 3	2 3 6	2 2 2	2 3 8	2 3 5	1 9 5	2 1 5	2 4 2	2 2 6	2 1 1	2 2 7
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, carcinoma																									
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS							+							+											+
Pelvic, chordoma														X											
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X										X		
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Interstitial cell, adenoma																				X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+	+	+	+				+								+	+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal				+		+	+	+	+															+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Fibroma																									
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Epithelial cell, thymoma malignant																									
Integumentary System																									
Mammary gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	I	+	+
Adenoma																									
Fibroadenoma																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Carcinoma, metastatic, Zymbal's gland																									
Keratoacanthoma							X				X	X	X	X		X				X					
Squamous cell papilloma			X						X															X	
Squamous cell papilloma, multiple																									
Trichoepithelioma										X															
Sebaceous gland, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	5 7 7	5 8 5	5 8 6	5 9 8	6 0 4	6 0 8	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 0	6 4 3	6 4 7	6 5 4	6 5 8	6 6 2	6 6 2	6 7 0	6 8 1	6 8 2	6 8 7	6 9 0	6 9 5	6 9 7	7 0 9	7 1 1	7 2 3	7 3 3	7 3 6	
Carcass ID Number	2 2 9	2 3 4	2 4 1	2 2 1	2 3 2	2 4 3	2 3 1	2 0 7	2 1 7	2 1 2	2 1 2	2 4 4	1 9 1	2 3 0	2 1 0	1 9 7	2 0 2	2 2 7	2 0 1	1 4 0	1 9 8	1 1 6	1 1 9	2 0 8	2 2 5	2 9 5	1 9 3	2 1 9	2 1 3	2 3 9	Total Tissues/ Tumors
Endocrine System (continued)																															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Bilateral, C-cell, carcinoma													X																		1
C-cell, adenoma																					X							X	X		3
C-cell, carcinoma					X							X											X								2
Follicular cell, adenoma						X					X																				2
Follicular cell, carcinoma														X																	1
General Body System																															
Tissue NOS								+											+						+						6
Pelvic, chordoma																															1
Genital System																															
Coagulating gland				+																						+					2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Adenoma					X																						X				4
Carcinoma														X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
Interstitial cell, adenoma						X										X															3
Hematopoietic System																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Lymph node			+				+	+	+	+	+	+	+	+	+				+	+		+		+			+		+	+	27
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	55
Lymph node, mediastinal			+				+	+	+	+	+	+		+					+	+		+		+			+		+	+	23
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Fibroma								X																							1
Sarcoma																														X	1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	53
Epithelial cell, thymoma malignant		X																													1
Integumentary System																															
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X																													1
Fibroadenoma																X	X	X							X		X				6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	54
Basal cell adenoma																							X	X				X			3
Basal cell carcinoma																									X	X					2
Carcinoma, metastatic, Zymbal's gland				X																											1
Keratoacanthoma			X						X						X		X				X	X			X		X		X		16
Squamous cell papilloma																	X														4
Squamous cell papilloma, multiple																														X	1
Trichoepithelioma																															1
Sebaceous gland, adenoma															X									X							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	1 4 9	3 8 1	3 9 3	4 3 2	4 5 1	4 7 1	4 9 5	5 0 9	5 1 3	5 1 6	5 2 3	5 4 1	5 4 2	5 4 4	5 4 9	5 5 6	5 6 7	5 6 7	5 6 7	5 7 8	5 7 0	5 7 0	5 7 4	5 7 6	5 7 6
Carcass ID Number	2 4 7	2 0 9	1 9 2	2 3 8	2 0 0	2 1 4	1 9 4	2 0 8	2 2 3	2 0 3	2 0 6	2 0 4	2 0 4	2 2 4	2 1 6	2 3 3	2 3 6	2 2 2	2 3 8	1 9 5	2 1 5	2 4 2	2 2 6	2 1 1	2 3 7
Integumentary System (continued)																									
Skin (continued)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Subcutaneous tissue, fibroma		X				X						X							X					X	
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, sarcoma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+		+																		
Thymoma malignant, metastatic																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+																				
Spinal cord					+																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, multiple, metastatic, thyroid gland																									
Carcinoma, metastatic, Zymbal's gland										X															
Chordoma, metastatic, tissue NOS														X											
Sarcoma																X									
Thymoma malignant, metastatic, thymus																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland										+						+						+			
Adenoma																X						X			
Carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																							X		
Transitional epithelium, papilloma																				X					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X	X		X	X	X						X		X	X		X	X
Mesothelioma malignant							X											X	X	X					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7	
	7 8 8 9 0 0 1 1 1 1 2 2 4 4 5 5 6 6 7 8 8 8 9 9 9 0 1 2 3 3	
	7 5 6 8 4 8 0 9 9 9 0 0 3 7 4 8 2 2 0 1 2 7 0 5 7 9 1 3 3 6	
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 1 2 2 1 2 2 2 2 1 1 1 2 2 2 1 2 2 2	Total
	2 3 4 2 3 4 3 0 1 2 1 4 9 3 1 9 0 2 0 4 9 9 9 1 0 2 9 1 1 3	Tissues/
	9 4 1 1 2 3 1 7 7 0 2 4 1 0 0 7 2 7 1 0 8 6 9 8 5 5 3 9 3 9	Tumors
Integumentary System (continued)		
Skin (continued)	+ +	54
Subcutaneous tissue, fibroma	X X X X X	9
Subcutaneous tissue, fibroma, multiple	X X X X X X	6
Subcutaneous tissue, hemangiosarcoma	X	1
Subcutaneous tissue, sarcoma	X X	2
Subcutaneous tissue, sarcoma, multiple	X	1
Musculoskeletal System		
Bone	+ +	55
Skeletal muscle	+ +	4
Thymoma malignant, metastatic	X	1
Nervous System		
Brain	+ +	55
Peripheral nerve		1
Spinal cord		1
Respiratory System		
Lung	+ +	55
Alveolar/bronchiolar adenoma	X	1
Alveolar/bronchiolar carcinoma	X X X	2
Alveolar/bronchiolar carcinoma, multiple	X	1
Carcinoma, multiple, metastatic, thyroid gland	X	1
Carcinoma, metastatic, Zymbal's gland	X X	2
Chordoma, metastatic, tissue NOS		1
Sarcoma		1
Thymoma malignant, metastatic, thymus	X	1
Nose	+ +	55
Trachea	+ +	55
Special Senses System		
Zymbal's gland	+ +	5
Adenoma	X	3
Carcinoma	X	2
Urinary System		
Kidney	+ +	55
Renal tubule, adenoma	X X X	3
Urethra	+	1
Urinary bladder	+ +	55
Transitional epithelium, carcinoma		1
Transitional epithelium, papilloma	X	2
Systemic Lesions		
Multiple organs	+ +	55
Leukemia mononuclear	X X X X X X X X X X X X X X X X X X X X X X X X X X X X	34
Mesothelioma malignant	X X X X X	9

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure)

Number of Days on Study	2 2 2	3 6 5	3 6 6	3 8 8	3 9 6	4 0 2	4 1 0	4 2 4	4 2 5	4 3 2	4 3 2	4 3 9	4 5 1	4 7 1	4 7 1	4 9 0	5 0 7	5 0 7	5 1 1	5 1 3	5 1 3	5 1 6	5 1 6	5 1 9	5 2 0	5 2 1	5 2 2	5 2 2	5 2 7	5 3 0
Carcass ID Number	2 6 4	3 1 0	2 7 2	2 9 5	3 0 2	2 7 9	2 9 2	2 7 3	3 0 4	2 6 5	2 7 8	3 0 1	2 5 1	2 5 3	2 9 9	2 9 1	2 6 1	2 6 7	2 6 6	2 6 4	2 9 8	2 5 6	2 7 1	2 8 0	2 7 7	2 9 3	2 6 9	2 8 3	3 0 9	3 0 6
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																														
Carcinoma, multiple							X																							
Polyp adenomatous						X														X	X								X	
Polyp adenomatous, multiple											X																			
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous		X																												
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																											
Polyp adenomatous																														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																														
Squamous cell carcinoma, metastatic, lung		X																												
Mucosa, carcinoma																														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																														
Mesentery		+	+		+			+		+		+	+		+		+	+	+		+	+	+	+		+	+	+		
Carcinoma, metastatic, seminal vesicle																										X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																												
Acinar cell, adenoma																	X			X										
Acinar cell, adenoma, multiple																														
Pharynx																						+	+					+		
Palate, squamous cell carcinoma																							X							
Palate, squamous cell papilloma																						X	X					X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X											
Mucosa, squamous cell papilloma																														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue			+																+	+			+		+					
Squamous cell papilloma																			X	X					X					
Squamous cell papilloma, multiple																														
Tooth			+																											
Cardiovascular System																														
Blood vessel																			+							+				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle																										X				
Squamous cell carcinoma, metastatic, lung		X																												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	5 3 7	5 7 2	5 7 5	5 7 6	5 7 9	5 8 5	5 8 6	5 9 1	5 9 2	5 9 2	6 0 5	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 1	6 2 5	6 4 7	6 5 3	6 5 4	6 5 9	6 5 9	6 6 0	6 6 3	6 7 7	7 0 3	7 0 4	7 0 4	7 2 6	
Carcass ID Number	2 8 6	3 0 7	2 5 9	2 8 5	3 0 0	2 5 5	2 6 3	2 7 4	2 5 7	3 0 3	2 8 9	2 8 4	2 5 8	2 8 1	2 8 2	2 6 8	3 0 8	2 9 7	2 7 6	2 6 0	2 9 0	2 5 4	2 7 0	2 5 2	2 8 8	3 8 7	3 0 5	2 6 2	2 9 6	2 7 5	Total Tissues/ Tumors
Alimentary System																														
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Carcinoma																							X							1
Carcinoma, multiple																														1
Polyp adenomatous							X							X					X				X							8
Polyp adenomatous, multiple																														1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Polyp adenomatous																														1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Squamous cell carcinoma, metastatic, lung																														1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Carcinoma													X																	2
Polyp adenomatous	X																													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Carcinoma				X																										1
Squamous cell carcinoma, metastatic, lung																														1
Mucosa, carcinoma							X																							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma																				X										1
Mesentery		+	+	+	+	+				+								+			+	+				+	+	+		30
Carcinoma, metastatic, seminal vesicle																														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Squamous cell carcinoma, metastatic, lung																														1
Acinar cell, adenoma																														2
Acinar cell, adenoma, multiple						X																								1
Pharynx							+						+		+	+								+		+	+			10
Palate, squamous cell carcinoma																X														2
Palate, squamous cell papilloma							X								X									X			X			7
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Squamous cell papilloma							X							X		X														4
Mucosa, squamous cell papilloma																						X								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Tongue							+							+											+				+	9
Squamous cell papilloma														X															X	5
Squamous cell papilloma, multiple							X																							1
Tooth														+																2
Cardiovascular System																														
Blood vessel																														2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, seminal vesicle																														1
Squamous cell carcinoma, metastatic, lung																														1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	2 2 2	3 6 5	3 6 6	3 8 8	3 9 6	4 0 2	4 1 0	4 2 4	4 2 5	4 3 2	4 3 2	4 3 9	4 5 1	4 7 1	4 7 1	4 9 0	5 0 7	5 0 7	5 1 1	5 1 3	5 1 3	5 1 6	5 1 6	5 1 9	5 2 0	5 2 1	5 2 2	5 2 2	5 2 7	5 3 0
Carcass ID Number	2 6 4	3 1 0	2 7 2	2 9 5	3 0 2	2 7 9	2 9 2	3 7 3	3 0 4	2 6 5	2 7 8	3 0 1	2 5 1	2 5 3	2 9 9	2 9 1	2 6 1	2 6 7	2 6 6	2 9 4	2 9 8	2 5 6	2 7 1	2 8 0	2 7 7	2 9 3	2 6 9	2 8 3	3 0 9	3 0 6
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma																		X		X										
Pars intermedia, adenoma																														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X													X			
Follicular cell, adenoma										X							X								X					
Follicular cell, carcinoma				X																										
General Body System																														
Tissue NOS																														
Genital System																														
Coagulating gland																		+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle																											X			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																														
Carcinoma																											X			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X	X		X		X	X		X	X	X	X	X	X		X		X	X		X	X	X	X	X	X	X
Interstitial cell, adenoma						X		X			X							X		X			X							
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+				+								+	+	+	+				+		+	+					
Mediastinal, mesothelioma malignant, metastatic, mesentery																														
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal		+	+				+								+	+	+	+				+		+						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, seminal vesicle																											X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epithelial cell, thymoma NOS																														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	5 3 7	5 7 2	5 7 5	5 7 6	5 7 9	5 8 5	5 8 6	5 9 1	5 9 2	5 9 2	6 0 5	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 1	6 2 5	6 4 7	6 5 3	6 5 4	6 5 9	6 5 9	6 6 0	6 6 3	6 7 7	7 0 3	7 0 4	7 0 4	7 2 6	
Carcass ID Number	2 8 6	3 0 7	2 0 5 9	2 8 5	3 0 0	2 5 5	2 6 3	2 7 4	2 5 7	3 0 3	2 0 9	2 8 4	2 5 8	2 8 1	2 8 2	2 6 8	3 0 8	2 9 7	2 7 6	2 6 0	2 9 0	2 5 4	2 7 0	2 5 2	2 8 8	2 8 7	3 0 5	2 6 2	2 9 6	2 9 5	Total Tisses/ Tumors
Endocrine System																														
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma, metastatic, lung																														1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	58
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma					X												X											X		5
Pars intermedia, adenoma														X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
C-cell, adenoma												X							X											4
Follicular cell, adenoma										X	X												X			X				7
Follicular cell, carcinoma																											X			2
General Body System																														
Tissue NOS					+		+											+		+	+	+	+				+			8
Genital System																														
Coagulating gland														+			+													3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma																						X						X	X	4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, seminal vesicle																														1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Adenoma																								X						1
Carcinoma																														1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	52
Interstitial cell, adenoma						X																								7
Hematopoietic System																														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Lymph node		+		+	+				+	+	+	+	+	+	+		+	+	+	+	+	+	+					+	+	30
Mediastinal, mesothelioma malignant, metastatic, mesentery																						X								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mediastinal		+		+	+				+	+	+	+	+	+	+		+	+	+	+	+	+						+	+	27
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, seminal vesicle																														1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	57
Epithelial cell, thymoma NOS																				X										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	2 2 2	3 6 5	3 6 6	3 8 8	3 9 6	4 0 2	4 1 0	4 2 4	4 2 5	4 3 2	4 3 2	4 3 9	4 5 1	4 7 1	4 7 1	4 9 0	5 0 7	5 0 7	5 1 1	5 1 3	5 1 3	5 1 6	5 1 6	5 1 9	5 2 0	5 2 1	5 2 2	5 2 2	5 2 7	5 3 0
Carcass ID Number	2 6 4	3 1 0	2 7 2	2 9 5	3 0 2	2 7 9	2 9 2	2 7 3	3 0 4	2 6 5	2 7 8	3 0 1	2 5 1	2 5 3	2 9 9	2 9 1	2 6 1	2 6 7	2 6 6	2 6 6	2 9 4	2 9 8	2 5 6	2 7 1	2 8 0	2 7 7	2 9 3	2 6 9	2 8 3	3 0 9	3 0 6
Integumentary System																														
Mammary gland	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	I	+
Fibroadenoma																														
Fibroadenoma, multiple																														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																								X						
Keratoacanthoma																		X												
Keratoacanthoma, multiple																														
Squamous cell carcinoma																														
Squamous cell papilloma									X																	X		X	X	
Squamous cell papilloma, multiple																														
Trichoepithelioma																														
Sebaceous gland, adenoma																														
Subcutaneous tissue, fibroma				X											X		X							X						
Subcutaneous tissue, fibrosarcoma																														
Subcutaneous tissue, sarcoma												X																		
Musculoskeletal System																														
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+			+													+												
Hemangiosarcoma					X																									
Squamous cell carcinoma, metastatic, lung		X																												
Nervous System																														
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																												
Respiratory System																														
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X										
Alveolar/bronchiolar carcinoma																														
Alveolar/bronchiolar carcinoma, multiple																											X			
Carcinoma, multiple, metastatic, seminal vesicle																											X			
Carcinoma, metastatic, Zymbal's gland																														
Mesothelioma malignant, metastatic, mesentery																														
Squamous cell carcinoma		X																								X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																														
Eye																														
Zymbal's gland	+					+	+			+	+			+		+				+										+
Adenoma																				X										
Carcinoma	X					X	X			X	X					X				X										X
Bilateral, carcinoma														X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	5 3 7	5 7 2	5 7 5	5 7 6	5 7 9	5 8 5	5 8 6	5 9 1	5 9 2	5 9 2	6 0 5	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 1	6 2 5	6 4 7	6 5 3	6 5 4	6 5 9	6 5 9	6 6 0	6 6 3	6 7 7	7 0 3	7 0 4	7 0 4	7 2 6	
Carcass ID Number	2 8 6	3 0 7	2 5 9	2 8 5	3 0 0	2 5 5	2 6 3	2 7 4	2 7 7	2 5 3	2 8 9	2 8 4	2 5 8	2 8 1	2 8 2	2 6 8	3 0 8	2 9 7	2 7 6	2 6 0	2 9 0	2 5 4	2 7 0	2 5 2	2 8 8	2 8 7	3 0 5	2 6 2	2 9 6	2 7 5	Total Tissues/ Tumors
Integumentary System																															
Mammary gland	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	50
Fibroadenoma										X													X		X		X				4
Fibroadenoma, multiple																										X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Basal cell adenoma								X		X													X		X			X			6
Keratoacanthoma							X		X	X							X				X				X	X		X			9
Keratoacanthoma, multiple	X																														1
Squamous cell carcinoma																														X	1
Squamous cell papilloma													X				X	X					X		X	X					10
Squamous cell papilloma, multiple																				X											1
Trichoepithelioma																										X					1
Sebaceous gland, adenoma																				X				X							2
Subcutaneous tissue, fibroma													X							X		X									7
Subcutaneous tissue, fibrosarcoma			X																												1
Subcutaneous tissue, sarcoma										X																					2
Musculoskeletal System																															
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle																		+													4
Hemangiosarcoma																															1
Squamous cell carcinoma, metastatic, lung																															1
Nervous System																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma, metastatic, lung																															1
Respiratory System																															
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma								X													X									X	4
Alveolar/bronchiolar carcinoma															X									X							2
Alveolar/bronchiolar carcinoma, multiple																															1
Carcinoma, multiple, metastatic, seminal vesicle																															1
Carcinoma, metastatic, Zymbal's gland																								X							1
Mesothelioma malignant, metastatic, mesentery																						X									1
Squamous cell carcinoma																				X											3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Special Senses System																															
Eye			+																												1
Zymbal's gland	+		+									+	+		+									+							15
Adenoma													X																		2
Carcinoma	X		X									X	X		X																13
Bilateral, carcinoma																								X							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	2 2 2	3 6 5	3 6 6	3 8 8	3 9 6	4 0 2	4 1 0	4 2 4	4 2 5	4 3 2	4 3 2	4 3 9	4 5 1	4 7 1	4 7 1	4 9 0	5 0 7	5 0 7	5 1 1	5 1 3	5 1 3	5 1 6	5 1 6	5 1 9	5 2 0	5 2 1	5 2 2	5 2 2	5 2 7	5 3 0
Carcass ID Number	2 6 4	3 1 0	2 7 2	2 9 5	3 0 2	2 7 9	2 9 2	2 7 3	3 0 4	2 6 5	2 7 8	3 0 1	2 5 1	2 5 3	2 9 9	2 9 1	2 6 1	2 6 7	2 6 6	2 9 4	2 9 8	2 5 6	2 7 1	2 8 0	2 7 7	2 9 3	2 6 9	2 8 3	3 0 9	3 0 6
Urinary System																														
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, lung		X																												
Pelvis, transitional epithelium, carcinoma																														
Renal tubule, adenoma																														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																														
Transitional epithelium, papilloma																														
Systemic Lesions																														
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X											X				X			X	X		X	
Mesothelioma malignant		X			X						X		X			X		X	X	X		X		X	X			X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 20,000 ppm (Stop-Exposure) (continued)

Number of Days on Study	5 3 7	5 7 2	5 7 5	5 7 6	5 7 9	5 8 5	5 8 6	5 9 1	5 9 2	5 9 2	6 0 5	6 1 0	6 1 9	6 1 9	6 1 9	6 2 0	6 2 1	6 2 5	6 4 7	6 5 3	6 5 4	6 5 9	6 5 9	6 6 0	6 6 3	6 7 7	7 0 3	7 0 4	7 0 4	7 2 6	
Carcass ID Number	2 8 6	3 0 7	2 5 9	2 8 5	3 0 0	2 5 5	2 6 3	2 7 4	2 5 7	3 0 3	2 8 9	2 8 4	2 5 8	2 8 1	2 8 2	2 6 8	3 0 8	2 9 7	2 7 6	2 6 0	2 9 0	2 5 4	2 7 0	2 5 2	2 8 8	2 8 7	3 0 5	2 6 2	2 9 6	2 9 7	Total Tissues/ Tumors
Urinary System																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Squamous cell carcinoma, metastatic, lung																															1
Pelvis, transitional epithelium, carcinoma																												X			1
Renal tubule, adenoma																X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	59
Transitional epithelium, carcinoma																									X						1
Transitional epithelium, papilloma																								X							1
Systemic Lesions																															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear		X			X				X	X	X	X	X	X	X		X		X	X	X		X	X		X		X	X		25
Mesothelioma malignant		X	X		X	X	X										X	X		X	X	X	X				X	X	X		26

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	6/51 (12%)	12/53 (23%)	4/51 (8%)	4/54 (7%)
Adjusted rate[b]	19.6%	42.2%	18.5%	18.3%
Terminal rate[c]	3/26 (12%)	6/20 (30%)	1/13 (8%)	0/1 (0%)
First incidence (days)	628	543	656	576
Life table test[d]	P=0.121	P=0.040	P=0.562	P=0.090
Logistic regression test[d]	P=0.353N	P=0.059	P=0.488N	P=0.631N
Cochran-Armitage test[d]	P=0.099N			
Fisher exact test[d]		P=0.113	P=0.370N	P=0.335N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	3/51 (6%)	3/53 (6%)	1/51 (2%)	1/54 (2%)
Adjusted rate	11.0%	14.1%	2.7%	3.3%
Terminal rate	2/26 (8%)	2/20 (10%)	0/13 (0%)	0/1 (0%)
First incidence (days)	725	725	641	577
Life table test	P=0.507	P=0.540	P=0.504N	P=0.520
Logistic regression test	P=0.389N	P=0.549	P=0.381N	P=0.598N
Cochran-Armitage test	P=0.154N			
Fisher exact test		P=0.642N	P=0.309N	P=0.288N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	9/51 (18%)	14/53 (26%)	5/51 (10%)	5/54 (9%)
Adjusted rate	29.2%	48.8%	20.7%	21.2%
Terminal rate	5/26 (19%)	7/20 (35%)	1/13 (8%)	0/1 (0%)
First incidence (days)	628	543	641	576
Life table test	P=0.116	P=0.067	P=0.563N	P=0.058
Logistic regression test	P=0.263N	P=0.089	P=0.307N	P=0.528N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.201	P=0.194N	P=0.165N
Esophagus: Squamous Cell Papilloma				
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	5/55 (9%)
Adjusted rate	0.0%	0.0%	3.2%	62.6%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—[e]	—	662	549
Life table test	P<0.001	—	P=0.454	P<0.001
Logistic regression test	P=0.001	—	P=0.507	P=0.021
Cochran-Armitage test	P=0.002			
Fisher exact test		—	P=0.500	P=0.034
Intestine (Large): Adenomatous Polyp				
Overall rate	0/51 (0%)	0/53 (0%)	3/51 (6%)	4/55 (7%)
Adjusted rate	0.0%	0.0%	15.3%	46.0%
Terminal rate	0/26 (0%)	0/20 (0%)	1/13 (8%)	0/1 (0%)
First incidence (days)	—	—	684	495
Life table test	P<0.001	—	P=0.055	P=0.003
Logistic regression test	P=0.006	—	P=0.086	P=0.063
Cochran-Armitage test	P=0.014			
Fisher exact test		—	P=0.121	P=0.069

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Kidney (Renal Tubule): Adenoma				
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	3/55 (5%)
Adjusted rate	0.0%	0.0%	4.5%	41.7%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	—	695	690
Life table test	P<0.001	—	P=0.413	P<0.001
Logistic regression test	P=0.001	—	P=0.482	P=0.009
Cochran-Armitage test	P=0.024			
Fisher exact test		—	P=0.500	P=0.136
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/51 (2%)	0/53 (0%)	3/51 (6%)	1/55 (2%)
Adjusted rate	2.9%	0.0%	18.6%	10.0%
Terminal rate	0/26 (0%)	0/20 (0%)	2/13 (15%)	0/1 (0%)
First incidence (days)	696	—	684	682
Life table test	P=0.053	P=0.554N	P=0.143	P=0.408
Logistic regression test	P=0.182	P=0.515N	P=0.211	P=0.644
Cochran-Armitage test	P=0.491			
Fisher exact test		P=0.490N	P=0.309	P=0.733N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/51 (0%)	1/53 (2%)	0/51 (0%)	3/55 (5%)
Adjusted rate	0.0%	5.0%	0.0%	59.3%
Terminal rate	0/26 (0%)	1/20 (5%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	736 (T)	—	620
Life table test	P<0.001	P=0.448	—	P=0.001
Logistic regression test	P=0.005	P=0.448	—	P=0.024
Cochran-Armitage test	P=0.050			
Fisher exact test		P=0.510	—	P=0.136
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/51 (2%)	1/53 (2%)	3/51 (6%)	4/55 (7%)
Adjusted rate	2.9%	5.0%	18.6%	63.4%
Terminal rate	0/26 (0%)	1/20 (5%)	2/13 (15%)	0/1 (0%)
First incidence (days)	696	736 (T)	684	620
Life table test	P<0.001	P=0.700	P=0.143	P=0.001
Logistic regression test	P=0.003	P=0.726	P=0.211	P=0.029
Cochran-Armitage test	P=0.088			
Fisher exact test		P=0.743N	P=0.309	P=0.206
Mammary Gland: Fibroadenoma				
Overall rate	0/51 (0%)	4/53 (8%)	6/51 (12%)	6/55 (11%)
Adjusted rate	0.0%	18.9%	42.6%	51.6%
Terminal rate	0/26 (0%)	3/20 (15%)	5/13 (38%)	0/1 (0%)
First incidence (days)	—	725	726	576
Life table test	P<0.001	P=0.036	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.034	P<0.001	P=0.003
Cochran-Armitage test	P=0.035			
Fisher exact test		P=0.064	P=0.013	P=0.017

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	0/51 (0%)	4/53 (8%)	7/51 (14%)	7/55 (13%)
Adjusted rate	0.0%	18.9%	44.8%	53.2%
Terminal rate	0/26 (0%)	3/20 (15%)	5/13 (38%)	0/1 (0%)
First incidence (days)	—	725	684	576
Life table test	P<0.001	P=0.036	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.034	P<0.001	P=0.002
Cochran-Armitage test	P=0.017			
Fisher exact test		P=0.064	P=0.006	P=0.008
Oral Cavity (Tongue, Pharynx, or Tooth): Squamous Cell Papilloma				
Overall rate	0/51 (0%)	4/53 (8%)	8/51 (16%)	10/55 (18%)
Adjusted rate	0.0%	20.0%	35.7%	44.2%
Terminal rate	0/26 (0%)	4/20 (20%)	3/13 (23%)	0/1 (0%)
First incidence (days)	—	736 (T)	536	381
Life table test	P<0.001	P=0.033	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.033	P=0.004	P=0.005
Cochran-Armitage test	P=0.001			
Fisher exact test		P=0.064	P=0.003	P<0.001
Oral Cavity (Tongue, Pharynx, or Tooth): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/51 (0%)	4/53 (8%)	9/51 (18%)	10/55 (18%)
Adjusted rate	0.0%	20.0%	39.0%	44.2%
Terminal rate	0/26 (0%)	4/20 (20%)	3/13 (23%)	0/1 (0%)
First incidence (days)	—	736 (T)	536	381
Life table test	P<0.001	P=0.033	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.033	P=0.002	P=0.005
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.064	P=0.001	P<0.001
Pancreas: Adenoma				
Overall rate	1/51 (2%)	2/53 (4%)	4/51 (8%)	3/53 (6%)
Adjusted rate	3.8%	10.0%	30.8%	34.1%
Terminal rate	1/26 (4%)	2/20 (10%)	4/13 (31%)	0/1 (0%)
First incidence (days)	736 (T)	736 (T)	736 (T)	604
Life table test	P<0.001	P=0.408	P=0.033	P=0.007
Logistic regression test	P=0.005	P=0.408	P=0.033	P=0.089
Cochran-Armitage test	P=0.232			
Fisher exact test		P=0.515	P=0.181	P=0.324
Pancreatic Islets: Adenoma				
Overall rate	1/51 (2%)	6/53 (11%)	0/51 (0%)	0/55 (0%)
Adjusted rate	3.8%	25.8%	0.0%	0.0%
Terminal rate	1/26 (4%)	4/20 (20%)	0/13 (0%)	0/1 (0%)
First incidence (days)	736 (T)	648	—	—
Life table test	P=0.598N	P=0.028	P=0.638N	P=0.993N
Logistic regression test	P=0.365N	P=0.031	P=0.638N	P=0.993N
Cochran-Armitage test	P=0.078N			
Fisher exact test		P=0.062	P=0.500N	P=0.481N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	1/51 (2%)	8/53 (15%)	1/51 (2%)	0/55 (0%)
Adjusted rate	3.8%	30.6%	2.0%	0.0%
Terminal rate	1/26 (4%)	4/20 (20%)	0/13 (0%)	0/1 (0%)
First incidence (days)	736 (T)	543	536	—
Life table test	P=0.530N	P=0.008	P=0.694	P=0.993N
Logistic regression test	P=0.139N	P=0.011	P=0.756N	P=0.993N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.018	P=0.752N	P=0.481N
Pharynx: Squamous Cell Papilloma				
Overall rate	0/51 (0%)	2/53 (4%)	3/51 (6%)	2/55 (4%)
Adjusted rate	0.0%	10.0%	13.5%	18.4%
Terminal rate	0/26 (0%)	2/20 (10%)	1/13 (8%)	0/1 (0%)
First incidence (days)	—	736 (T)	641	509
Life table test	P=0.009	P=0.182	P=0.069	P=0.085
Logistic regression test	P=0.132	P=0.182	P=0.112	P=0.295
Cochran-Armitage test	P=0.260			
Fisher exact test		P=0.257	P=0.121	P=0.267
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	9/51 (18%)	6/50 (12%)	6/53 (11%)
Adjusted rate	22.4%	34.2%	31.1%	70.2%
Terminal rate	3/25 (12%)	5/20 (25%)	3/13 (23%)	0/1 (0%)
First incidence (days)	675	512	576	604
Life table test	P=0.006	P=0.240	P=0.362	P=0.003
Logistic regression test	P=0.278	P=0.290	P=0.619	P=0.154
Cochran-Armitage test	P=0.301N			
Fisher exact test		P=0.410	P=0.500N	P=0.455N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	10/51 (20%)	6/50 (12%)	6/53 (11%)
Adjusted rate	22.4%	38.6%	31.1%	70.2%
Terminal rate	3/25 (12%)	6/20 (30%)	3/13 (23%)	0/1 (0%)
First incidence (days)	675	512	576	604
Life table test	P=0.006	P=0.165	P=0.362	P=0.003
Logistic regression test	P=0.284	P=0.197	P=0.619	P=0.154
Cochran-Armitage test	P=0.268N			
Fisher exact test		P=0.314	P=0.500N	P=0.455N
Preputial Gland: Adenoma				
Overall rate	3/51 (6%)	3/52 (6%)	4/51 (8%)	4/55 (7%)
Adjusted rate	11.5%	11.6%	19.5%	31.7%
Terminal rate	3/26 (12%)	1/20 (5%)	2/13 (15%)	0/1 (0%)
First incidence (days)	736 (T)	648	620	542
Life table test	P=0.007	P=0.546	P=0.237	P=0.017
Logistic regression test	P=0.233	P=0.565	P=0.412	P=0.366
Cochran-Armitage test	P=0.430			
Fisher exact test		P=0.652N	P=0.500	P=0.542

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	5/51 (10%)	4/52 (8%)	5/51 (10%)	5/55 (9%)
Adjusted rate	16.2%	16.2%	23.2%	35.7%
Terminal rate	3/26 (12%)	2/20 (10%)	2/13 (15%)	0/1 (0%)
First incidence (days)	628	648	620	542
Life table test	P=0.009	P=0.622	P=0.330	P=0.029
Logistic regression test	P=0.317	P=0.598N	P=0.580	P=0.507
Cochran-Armitage test	P=0.564			
Fisher exact test		P=0.488N	P=0.630N	P=0.580N
Skin: Squamous Cell Papilloma				
Overall rate	1/51 (2%)	0/53 (0%)	2/51 (4%)	5/55 (9%)
Adjusted rate	3.8%	0.0%	10.5%	100.0%
Terminal rate	1/26 (4%)	0/20 (0%)	1/13 (8%)	1/1 (100%)
First incidence (days)	736 (T)	—	654	393
Life table test	P<0.001	P=0.552N	P=0.319	P=0.003
Logistic regression test	P=0.024	P=0.552N	P=0.426	P=0.172
Cochran-Armitage test	P=0.018			
Fisher exact test		P=0.490N	P=0.500	P=0.121
Skin: Keratoacanthoma				
Overall rate	3/51 (6%)	5/53 (9%)	11/51 (22%)	16/55 (29%)
Adjusted rate	9.7%	23.6%	41.0%	83.0%
Terminal rate	2/26 (8%)	4/20 (20%)	2/13 (15%)	0/1 (0%)
First incidence (days)	619	725	633	495
Life table test	P<0.001	P=0.227	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.256	P=0.017	P=0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.380	P=0.021	P=0.002
Skin: Basal Cell Adenoma				
Overall rate	0/51 (0%)	1/53 (2%)	0/51 (0%)	3/55 (5%)
Adjusted rate	0.0%	2.9%	0.0%	62.5%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	659	—	690
Life table test	P<0.001	P=0.463	—	P<0.001
Logistic regression test	P=0.006	P=0.516	—	P=0.005
Cochran-Armitage test	P=0.050			
Fisher exact test		P=0.510	—	P=0.136
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/51 (2%)	0/53 (0%)	2/51 (4%)	5/55 (9%)
Adjusted rate	3.8%	0.0%	10.5%	100.0%
Terminal rate	1/26 (4%)	0/20 (0%)	1/13 (8%)	1/1 (100%)
First incidence (days)	736 (T)	—	654	393
Life table test	P<0.001	P=0.552N	P=0.319	P=0.003
Logistic regression test	P=0.024	P=0.552N	P=0.426	P=0.172
Cochran-Armitage test	P=0.018			
Fisher exact test		P=0.490N	P=0.500	P=0.121

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	0/51 (0%)	1/53 (2%)	2/51 (4%)	6/55 (11%)
Adjusted rate	0.0%	2.9%	8.7%	78.0%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	659	694	516
Life table test	P<0.001	P=0.463	P=0.155	P<0.001
Logistic regression test	P<0.001	P=0.516	P=0.215	P<0.001
Cochran-Armitage test	P=0.003			
Fisher exact test		P=0.510	P=0.248	P=0.017
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	4/51 (8%)	6/53 (11%)	14/51 (27%)	24/55 (44%)
Adjusted rate	13.5%	25.9%	50.4%	100.0%
Terminal	3/26 (12%)	4/20 (20%)	3/13 (23%)	1/1 (100%)
First incidence (days)	619	659	633	393
Life table test	P<0.001	P=0.227	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.267	P=0.006	P<0.001
Cochran-Armitage	P<0.001			
Fisher exact test		P=0.395	P=0.009	P<0.001
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/51 (4%)	8/53 (15%)	11/51 (22%)	15/55 (27%)
Adjusted rate	6.3%	26.5%	35.2%	100.0%
Terminal rate	1/26 (4%)	3/20 (15%)	1/13 (8%)	1/1 (100%)
First incidence (days)	660	576	536	381
Life table test	P<0.001	P=0.026	P=0.003	P<0.001
Logistic regression test	P=0.001	P=0.047	P=0.010	P=0.001
Cochran-Armitage test	P=0.001			
Fisher exact test		P=0.053	P=0.007	P<0.001
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/51 (0%)	0/53 (0%)	2/51 (4%)	3/55 (5%)
Adjusted rate	0.0%	0.0%	6.2%	56.5%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	—	621	577
Life table test	P<0.001	—	P=0.203	P=0.004
Logistic regression test	P=0.017	—	P=0.247	P=0.052
Cochran-Armitage test	P=0.033			
Fisher exact test		—	P=0.248	P=0.136
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/51 (0%)	1/53 (2%)	2/51 (4%)	3/55 (5%)
Adjusted rate	0.0%	5.0%	6.2%	56.5%
Terminal rate	0/26 (0%)	1/20 (5%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	736 (T)	621	577
Life table test	P<0.001	P=0.448	P=0.203	P=0.004
Logistic regression test	P=0.026	P=0.448	P=0.247	P=0.052
Cochran-Armitage test	P=0.071			
Fisher exact test		P=0.510	P=0.248	P=0.136

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	2/51 (4%)	9/53 (17%)	13/51 (25%)	16/55 (29%)
Adjusted rate	6.3%	30.8%	39.3%	100.0%
Terminal rate	1/26 (4%)	4/20 (20%)	1/13 (8%)	1/1 (100%)
First incidence (days)	660	576	536	381
Life table test	P<0.001	P=0.013	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.025	P=0.003	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.030	P=0.002	P<0.001
Testes: Adenoma				
Overall rate	49/51 (96%)	48/53 (91%)	51/51 (100%)	51/55 (93%)
Adjusted rate	100.0%	95.9%	100.0%	100.0%
Terminal rate	26/26 (100%)	18/20 (90%)	13/13 (100%)	1/1 (100%)
First incidence (days)	467	450	451	432
Life table test	P<0.001	P=0.139	P=0.002	P<0.001
Logistic regression test	P=0.566N	P=0.361N	P=0.311	P=0.497
Cochran-Armitage test	P=0.470N			
Fisher exact test		P=0.235N	P=0.248	P=0.376N
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/51 (14%)	4/53 (8%)	4/51 (8%)	3/55 (5%)
Adjusted rate	23.1%	18.4%	20.4%	70.0%
Terminal rate	5/26 (19%)	3/20 (15%)	2/13 (15%)	0/1 (0%)
First incidence (days)	619	711	641	682
Life table test	P=0.099	P=0.418N	P=0.593N	P=0.072
Logistic regression test	P=0.490	P=0.367N	P=0.358N	P=0.507
Cochran-Armitage test	P=0.119N			
Fisher exact test		P=0.241N	P=0.263N	P=0.131N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	1/51 (2%)	1/53 (2%)	1/51 (2%)	3/55 (5%)
Adjusted rate	3.4%	4.0%	3.2%	20.5%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	722	711	662	604
Life table test	P=0.010	P=0.710	P=0.667	P=0.030
Logistic regression test	P=0.095	P=0.726	P=0.752	P=0.186
Cochran-Armitage test	P=0.181			
Fisher exact test		P=0.743N	P=0.752N	P=0.338
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/51 (16%)	4/53 (8%)	5/51 (10%)	6/55 (11%)
Adjusted rate	25.7%	18.4%	23.0%	76.2%
Terminal rate	5/26 (19%)	3/20 (15%)	2/13 (15%)	0/1 (0%)
First incidence (days)	619	711	641	604
Life table test	P=0.004	P=0.320N	P=0.604	P=0.003
Logistic regression test	P=0.171	P=0.270N	P=0.373N	P=0.212
Cochran-Armitage test	P=0.379N			
Fisher exact test		P=0.161N	P=0.277N	P=0.330N

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	0/51 (0%)	1/53 (2%)	4/51 (8%)	1/55 (2%)
Adjusted rate	0.0%	2.6%	20.8%	5.9%
Terminal rate	0/26 (0%)	0/20 (0%)	2/13 (15%)	0/1 (0%)
First incidence (days)	—	610	633	647
Life table test	P=0.041	P=0.462	P=0.023	P=0.325
Logistic regression test	P=0.235	P=0.549	P=0.047	P=0.492
Cochran-Armitage test	P=0.361			
Fisher exact test		P=0.510	P=0.059	P=0.519
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/51 (0%)	2/53 (4%)	6/51 (12%)	3/55 (5%)
Adjusted rate	0.0%	7.5%	27.5%	14.2%
Terminal rate	0/26 (0%)	1/20 (5%)	2/13 (15%)	0/1 (0%)
First incidence (days)	—	610	633	608
Life table test	P=0.001	P=0.191	P=0.004	P=0.027
Logistic regression test	P=0.055	P=0.239	P=0.013	P=0.124
Cochran-Armitage test	P=0.133			
Fisher exact test		P=0.257	P=0.013	P=0.136
Tongue: Squamous Cell Papilloma				
Overall rate	0/51 (0%)	2/53 (4%)	5/51 (10%)	8/55 (15%)
Adjusted rate	0.0%	10.0%	24.5%	31.6%
Terminal rate	0/26 (0%)	2/20 (10%)	2/13 (15%)	0/1 (0%)
First incidence (days)	—	736 (T)	536	381
Life table test	P<0.001	P=0.182	P=0.009	P<0.001
Logistic regression test	P=0.002	P=0.182	P=0.032	P=0.016
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.257	P=0.028	P=0.004
Urinary Bladder: Transitional Cell Papilloma or Carcinoma				
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	3/55 (5%)
Adjusted rate	0.0%	0.0%	7.7%	8.9%
Terminal rate	0/26 (0%)	0/20 (0%)	1/13 (8%)	0/1 (0%)
First incidence (days)	—	—	736 (T)	568
Life table test	P=0.002	—	P=0.362	P=0.069
Logistic regression test	P=0.034	—	P=0.362	P=0.206
Cochran-Armitage test	P=0.024			
Fisher exact test		—	P=0.500	P=0.136
Zymbal's Gland: Adenoma				
Overall rate	0/51 (0%)	0/53 (0%)	1/51 (2%)	3/55 (5%)
Adjusted rate	0.0%	0.0%	4.3%	52.6%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	—	—	694	556
Life table test	P=0.001	—	P=0.422	P=0.020
Logistic regression test	P=0.022	—	P=0.484	P=0.133
Cochran-Armitage test	P=0.024			
Fisher exact test		—	P=0.500	P=0.136

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Zymbal's Gland: Carcinoma				
Overall rate	2/51 (4%)	1/53 (2%)	3/51 (6%)	2/55 (4%)
Adjusted rate	4.1%	3.8%	7.2%	5.8%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	334	696	592	516
Life table test	P=0.286	P=0.554N	P=0.467	P=0.582
Logistic regression test	P=0.443N	P=0.351N	P=0.451	P=0.379N
Cochran-Armitage test	P=0.528			
Fisher exact test		P=0.485N	P=0.500	P=0.662N
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	2/51 (4%)	1/53 (2%)	4/51 (8%)	5/55 (9%)
Adjusted rate	4.1%	3.8%	11.2%	55.4%
Terminal rate	0/26 (0%)	0/20 (0%)	0/13 (0%)	0/1 (0%)
First incidence (days)	334	696	592	516
Life table test	P=0.009	P=0.554N	P=0.286	P=0.067
Logistic regression test	P=0.212	P=0.351N	P=0.312	P=0.503
Cochran-Armitage test	P=0.095			
Fisher exact test		P=0.485N	P=0.339	P=0.251
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/51 (53%)	29/53 (55%)	40/51 (78%)	34/55 (62%)
Adjusted rate	59.0%	76.3%	97.3%	100.0%
Terminal rate	8/26 (31%)	12/20 (60%)	12/13 (92%)	1/1 (100%)
First incidence (days)	467	480	536	432
Life table test	P<0.001	P=0.164	P<0.001	P<0.001
Logistic regression test	P=0.087	P=0.476	P=0.006	P=0.549
Cochran-Armitage test	P=0.129			
Fisher exact test		P=0.506	P=0.006	P=0.234
All Organs: Malignant Mesothelioma				
Overall rate	0/51 (0%)	3/53 (6%)	8/51 (16%)	9/55 (16%)
Adjusted rate	0.0%	7.7%	43.3%	100.0%
Terminal rate	0/26 (0%)	0/20 (0%)	4/13 (31%)	1/1 (100%)
First incidence (days)	—	586	681	495
Life table test	P<0.001	P=0.097	P<0.001	P<0.001
Logistic regression test	P<0.001	P=0.157	P<0.001	P=0.003
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.129	P=0.003	P=0.002
All Organs: Benign Neoplasms				
Overall rate	50/51 (98%)	52/53 (98%)	51/51 (100%)	54/55 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	26/26 (100%)	20/20 (100%)	13/13 (100%)	1/1 (100%)
First incidence (days)	467	450	451	381
Life table test	P<0.001	P=0.059	P=0.003	P<0.001
Logistic regression test	—[f]	—	—	—
Cochran-Armitage test	P=0.599			
Fisher exact test		P=0.743	P=0.500	P=0.733

TABLE A3a
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
All Organs: Malignant Neoplasms				
Overall rate	32/51 (63%)	36/53 (68%)	46/51 (90%)	49/55 (89%)
Adjusted rate	64.8%	82.8%	97.8%	100.0%
Terminal rate	9/26 (35%)	13/20 (65%)	12/13 (92%)	1/1 (100%)
First incidence (days)	334	450	451	432
Life table test	P<0.001	P=0.099	P<0.001	P<0.001
Logistic regression test	P=0.002	P=0.489	P=0.004	P=0.361
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.364	P<0.001	P=0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	51/51 (100%)	52/53 (98%)	51/51 (100%)	54/55 (98%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	26/26 (100%)	20/20 (100%)	13/13 (100%)	1/1 (100%)
First incidence (days)	334	450	451	381
Life table test	P<0.001	P=0.079	P=0.005	P<0.001
Logistic regression test	P=0.347N	P=0.500N	—	P=0.500N
Cochran-Armitage test	P=0.419N			
Fisher exact test		P=0.510N	P=1.000N	P=0.519N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, lung, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	20,000 ppm
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	6/51 (12%)	0/60 (0%)
Adjusted rate[b]	19.6%	0.0%
Terminal rate[c]	3/26 (12%)	0/0 (0%)
First incidence (days)	628	—[e]
Life table test[d]		P=0.673N
Logistic regression test[d]		P=0.239N
Fisher exact test[d]		P=0.008N
Adrenal Medulla: Malignant Pheochromocytoma		
Overall rate	3/51 (6%)	0/60 (0%)
Adjusted rate	11.0%	0.0%
Terminal rate	2/26 (8%)	0/0 (0%)
First incidence (days)	725	—
Life table test		P=0.995N
Logistic regression test		P=0.877N
Fisher exact test		P=0.094N
Adrenal Medulla: Benign or Malignant Pheochromocytoma		
Overall rate	9/51 (18%)	0/60 (0%)
Adjusted rate	29.2%	0.0%
Terminal rate	5/26 (19%)	0/0 (0%)
First incidence (days)	628	—
Life table test		P=0.637N
Logistic regression test		P=0.189N
Fisher exact test		P<0.001N
Intestine (Large): Adenomatous Polyp		
Overall rate	0/51 (0%)	10/60 (15%)
Adjusted rate	0.0%	34.7%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	402
Life table test		P<0.001
Logistic regression test		P=0.020
Fisher exact test		P=0.003
Intestine (Small): Carcinoma		
Overall rate	0/51 (0%)	4/60 (7%)
Adjusted rate	0.0%	14.3%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	366
Life table test		P=0.019
Logistic regression test		P=0.181
Fisher exact test		P=0.081

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	1/51 (2%)	4/60 (7%)
Adjusted rate	2.9%	100.0%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	696	513
Life table test		P=0.003
Logistic regression test		P=0.086
Fisher exact test		P=0.237
Lung: Alveolar/bronchiolar Carcinoma		
Overall rate	0/51 (0%)	3/60 (5%)
Adjusted rate	0.0%	21.4%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	522
Life table test		P=0.015
Logistic regression test		P=0.118
Fisher exact test		P=0.154
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	1/51 (2%)	7/60 (12%)
Adjusted rate	2.9%	100.0%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	696	513
Life table test		P<0.001
Logistic regression test		P=0.011
Fisher exact test		P=0.050
Lung: Squamous Cell Carcinoma		
Overall rate	0/51 (0%)	3/60 (5%)
Adjusted rate	0.0%	13.2%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	365
Life table test		P=0.052
Logistic regression test		P=0.330
Fisher exact test		P=0.154
Mammary Gland: Fibroadenoma		
Overall rate	0/51 (0%)	5/60 (8%)
Adjusted rate	0.0%	57.6%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	592
Life table test		P<0.001
Logistic regression test		P=0.001
Fisher exact test		P=0.043

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Oral Cavity (Pharynx or Tongue): Squamous Cell Papilloma		
Overall rate	0/51 (0%)	12/60 (20%)
Adjusted rate	0.0%	100.0%
Terminal rate	0/26 (0%)	0/0
First incidence (days)	—	511
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P<0.001
Oral Cavity (Pharynx or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma		
Overall rate	0/51 (0%)	13/60 (22%)
Adjusted rate	0.0%	100.0%
Terminal rate	0/26 (0%)	0/0
First incidence (days)	—	511
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P<0.001
Pancreas: Adenoma		
Overall rate	1/51 (2%)	3/59 (5%)
Adjusted rate	3.8%	8.5%
Terminal rate	1/26 (4%)	0/0 (0%)
First incidence (days)	736 (T)	507
Life table test		P=0.077
Logistic regression test		P=0.447
Fisher exact test		P=0.366
Pharynx: Squamous Cell Papilloma		
Overall rate	0/51 (0%)	7/60 (12%)
Adjusted rate	0.0%	46.5%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	516
Life table test		P<0.001
Logistic regression test		P=0.010
Fisher exact test		P=0.011
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	7/50 (14%)	5/57 (9%)
Adjusted rate	22.4%	43.2%
Terminal rate	3/25 (12%)	0/0 (0%)
First incidence (days)	675	507
Life table test		P=0.010
Logistic regression test		P=0.551
Fisher exact test		P=0.291N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Preputial Gland: Adenoma		
Overall rate	3/51 (6%)	4/60 (7%)
Adjusted rate	11.5%	100.0%
Terminal rate	3/26 (12%)	0/0 (0%)
First incidence (days)	736 (T)	659
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P=0.591
Preputial Gland: Adenoma or Carcinoma		
Overall rate	5/51 (10%)	4/60 (7%)
Adjusted rate	16.2%	100.0%
Terminal rate	3/26 (12%)	0/0 (0%)
First incidence (days)	628	659
Life table test		P<0.001
Logistic regression test		P=0.051
Fisher exact test		P=0.397N
Skin: Squamous Cell Papilloma		
Overall rate	1/51 (2%)	11/60 (18%)
Adjusted rate	3.8%	60.9%
Terminal rate	1/26 (4%)	0/0 (0%)
First incidence (days)	736 (T)	425
Life table test		P<0.001
Logistic regression test		P=0.002
Fisher exact test		P=0.005
Skin: Keratoacanthoma		
Overall rate	3/51 (6%)	10/60 (17%)
Adjusted rate	9.7%	69.4%
Terminal rate	2/26 (8%)	0/0 (0%)
First incidence (days)	619	507
Life table test		P<0.001
Logistic regression test		P=0.006
Fisher exact test		P=0.069
Skin: Basal Cell Adenoma		
Overall rate	0/51 (0%)	6/60 (10%)
Adjusted rate	0.0%	56.1%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	519
Life table test		P<0.001
Logistic regression test		P=0.005
Fisher exact test		P=0.022

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Skin: Trichoepithelioma or Basal Cell Adenoma		
Overall rate	0/51 (0%)	7/60 (12%)
Adjusted rate	0.0%	64.9%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	519
Life table test		P<0.001
Logistic regression test		P=0.001
Fisher exact test		P=0.011
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma		
Overall rate	1/51 (2%)	12/60 (20%)
Adjusted rate	3.8%	100.0%
Terminal rate	1/26 (4%)	0/0 (0%)
First incidence (days)	736 (T)	425
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P=0.003
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Squamous Cell Carcinoma		
Overall rate	4/51 (8%)	21/60 (35%)
Adjusted rate	13.5%	100.0%
Terminal rate	3/26 (12%)	0/0 (0%)
First incidence (days)	619	425
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P<0.001
Skin (Subcutaneous Tissue): Fibroma		
Overall rate	2/51 (4%)	7/60 (12%)
Adjusted rate	6.3%	30.2%
Terminal rate	1/26 (4%)	0/0
First incidence (days)	660	388
Life table test		P=0.002
Logistic regression test		P=0.200
Fisher exact test		P=0.126
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma		
Overall rate	0/51 (0%)	3/60 (5%)
Adjusted rate	0.0%	9.8%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	439
Life table test		P=0.058
Logistic regression test		P=0.277
Fisher exact test		P=0.154

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma		
Overall rate	2/51 (4%)	10/60 (17%)
Adjusted rate	6.3%	37.1%
Terminal rate	1/26 (4%)	0/0 (0%)
First incidence (days)	660	388
Life table test		P<0.001
Logistic regression test		P=0.079
Fisher exact test		P=0.029
Stomach (Forestomach): Squamous Cell Papilloma		
Overall rate	0/51 (0%)	5/60 (8%)
Adjusted rate	0.0%	26.7%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	511
Life table test		P=0.002
Logistic regression test		P=0.028
Fisher exact test		P=0.043
Testes: Adenoma		
Overall rate	49/51 (96%)	59/60 (98%)
Adjusted rate	100.0%	100.0%
Terminal rate	26/26 (100%)	0/0 (0%)
First incidence (days)	467	365
Life table test		P<0.001
Logistic regression test		P=0.039
Fisher exact test		P=0.439
Thyroid Gland (C-cell): Adenoma		
Overall rate	7/51 (14%)	4/59 (7%)
Adjusted rate	23.1%	17.5%
Terminal rate	5/26 (19%)	0/0 (0%)
First incidence (days)	619	471
Life table test		P=0.062
Logistic regression test		P=0.518N
Fisher exact test		P=0.186N
Thyroid Gland (C-cell): Adenoma or Carcinoma		
Overall rate	8/51 (16%)	4/59 (7%)
Adjusted rate	25.7%	17.5%
Terminal rate	5/26 (19%)	0/0 (0%)
First incidence (days)	619	471
Life table test		P=0.068
Logistic regression test		P=0.456N
Fisher exact test		P=0.118N

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	0/51 (0%)	7/59 (12%)
Adjusted rate	0.0%	39.9%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	432
Life table test		P<0.001
Logistic regression test		P=0.021
Fisher exact test		P=0.011
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	0/51 (0%)	9/59 (15%)
Adjusted rate	0.0%	55.7%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	388
Life table test		P<0.001
Logistic regression test		P=0.009
Fisher exact test		P=0.003
Tongue: Squamous Cell Papilloma		
Overall rate	0/51 (0%)	6/60 (10%)
Adjusted rate	0.0%	100.0%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	511
Life table test		P<0.001
Logistic regression test		P=0.028
Fisher exact test		P=0.022
Zymbal's Gland: Carcinoma		
Overall rate	2/51 (4%)	15/60 (25%)
Adjusted rate	4.1%	44.7%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	334	222
Life table test		P<0.001
Logistic regression test		P=0.166
Fisher exact test		P=0.002
Zymbal's Gland: Adenoma or Carcinoma		
Overall rate	2/51 (4%)	15/60 (25%)
Adjusted rate	4.1%	44.7%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	334	222
Life table test		P<0.001
Logistic regression test		P=0.166
Fisher exact test		P=0.002

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
All Organs: Mononuclear Cell Leukemia		
Overall rate	27/51 (53%)	25/60 (42%)
Adjusted rate	59.0%	92.5%
Terminal rate	8/26 (31%)	0/0 (0%)
First incidence (days)	467	366
Life table test		P<0.001
Logistic regression test		P=0.164N
Fisher exact test		P=0.160N
All Organs: Malignant Mesothelioma		
Overall rate	0/51 (0%)	26/60 (43%)
Adjusted rate	0.0%	91.5%
Terminal rate	0/26 (0%)	0/0 (0%)
First incidence (days)	—	365
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P<0.001
All Organs: Benign Neoplasms		
Overall rate	50/51 (98%)	59/60 (98%)
Adjusted rate	100.0%	100.0%
Terminal rate	26/26 (100%)	0/0
First incidence (days)	467	365
Life table test		P<0.001
Logistic regression test		P=0.638
Fisher exact test		P=0.710
All Organs: Malignant Neoplasms		
Overall rate	32/51 (63%)	55/60 (92%)
Adjusted rate	64.8%	100.0%
Terminal rate	9/26 (35%)	0/0 (0%)
First incidence (days)	334	222
Life table test		P<0.001
Logistic regression test		P=0.080
Fisher exact test		P<0.001

TABLE A3b
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	20,000 ppm
All Organs: Benign or Malignant Neoplasms		
Overall rate	51/51 (100%)	60/60 (100%)
Adjusted rate	100.0%	100.0%
Terminal rate	26/26 (100%)	0/0 (0%)
First incidence (days)	334	222
Life table test		P<0.001
Logistic regression test		—[f]
Fisher exact test		P=1.000N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreas, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the control group and the exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Epithelial Skin Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls			
	Basal Cell Adenoma	Basal Cell Carcinoma	Keratoacanthoma	Trichoepithelioma
Historical Incidence at Southern Research Institute				
Benzyl Acetate	0/50	0/50	5/50	0/50
C.I. Pigment Red 23	1/50	0/50	1/50	0/50
C.I. Pigment Red 3	1/50	0/50	2/50	1/50
Nitrofurantoin	0/50	3/50	4/50	0/50
o-Nitroanisole	1/50	0/50	3/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	3/50	0/50
Polysorbate 80	0/50	0/50	2/50	0/50
Rhodamine 6G	0/50	0/50	1/50	0/50
Roxarsone	0/50	0/50	4/50	0/50
Overall Historical Incidence				
Total	7/1,353 (0.5%)	8/1,353 (0.6%)	48/1,353 (3.6%)	2/1,353 (0.2%)
Standard deviation	1.1%	1.5%	2.6%	0.5%
Range	0%-4%	0%-6%	0%-10%	0%-2%

	Incidence in Controls (continued)		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Basal Cell Adenoma, Basal Cell Carcinoma, Keratoacanthoma, Trichoepithelioma, Squamous Cell Papilloma, or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	5/50
C.I. Pigment Red 23	1/50	1/50	4/50
C.I. Pigment Red 3	0/50	0/50	4/50
Nitrofurantoin	1/50	0/50	8/50
o-Nitroanisole	1/50	0/50	6/50
p-Nitrobenzoic Acid	0/50	0/50	3/50
Polysorbate 80	2/50	0/50	4/50
Rhodamine 6G	2/50	0/50	3/50
Roxarsone	0/50	1/50	5/50
Overall Historical Incidence			
Total	27/1,353 (2.0%)	9/1,353 (0.7%)	101/1,353 (7.5%)
Standard deviation	1.9%	1.1%	3.1%
Range	0%-8%	0%-4%	2%-16%

[a] Data as of 31 March 1993

TABLE A4b
Historical Incidence of Subcutaneous Tissue Skin Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls			
	Fibroma	Fibrosarcoma	Sarcoma	Fibroma, Neurofibroma, Neurofibrosarcoma, Fibrosarcoma, or Sarcoma
Historical Incidence at Southern Research Institute				
Benzyl Acetate	4/50	0/50	1/50	5/50
C.I. Pigment Red 23	0/50	0/50	0/50	0/50
C.I. Pigment Red 3	4/50	2/50	1/50	6/50
Nitrofurantoin	0/50	1/50	0/50	1/50
o-Nitroanisole	1/50	0/50	0/50	1/50
p-Nitrobenzoic Acid	4/50	1/50	1/50	6/50
Polysorbate 80	1/50	0/50	0/50	2/50
Rhodamine 6G	4/50	0/50	0/50	4/50
Roxarsone	1/50	2/50	0/50	3/50
Overall Historical Incidence				
Total	60/1,353 (4.4%)	18/1,353 (1.3%)	7/1,353 (0.5%)	89/1,353 (6.6%)
Standard deviation	4.1%	1.5%	0.9%	4.3%
Range	0%-12%	0%-4%	0%-2%	0%-16%

[a] Data as of 31 March 1993

TABLE A4c
Historical Incidence of Mammary Gland Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Fibroadenoma	Adenoma	Fibroadenoma or Adenoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	4/50	0/50	4/50
C.I. Pigment Red 23	2/50	0/50	2/50
C.I. Pigment Red 3	3/50	0/50	3/50
Nitrofurantoin	2/50	1/50	3/50
o-Nitroanisole	3/50	0/50	3/50
p-Nitrobenzoic Acid	2/50	0/50	2/50
Polysorbate 80	1/50	0/50	1/50
Rhodamine 6G	6/50	0/50	6/50
Roxarsone	2/50	0/50	2/50
Overall Historical Incidence			
Total	60/1,353 (4.4%)	3/1,353 (0.2%)	63/1,353 (4.7%)
Standard deviation	3.2%	0.6%	3.1%
Range	0%-12%	0%-2%	0%-12%

[a] Data as of 31 March 1993

TABLE A4d
Historical Incidence of Zymbal's Gland Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	1/50	1/50
C.I. Pigment Red 23	0/50	1/50	1/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	2/50	2/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	1/50	1/50	2/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	1/50	2/50
Overall Historical Incidence			
Total	2/1,353 (0.2%)	14/1,353 (1.0%)	16/1,353 (1.2%)
Standard deviation	0.5%	1.2%	1.4%
Range	0%-2%	0%-4%	0%-4%

[a] Data as of 31 March 1993

TABLE A4e
Historical Incidence of Pharynx Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	1/50	0/50	1/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	2/50	0/50	2/50
Overall Historical Incidence			
Total	5/1,353 (0.4%)	0/1,353 (0.0%)	5/1,353 (0.4%)
Standard deviation	1.0%		1.0%
Range	0%-4%		0%-4%

[a] Data as of 31 March 1993

TABLE A4f
Historical Incidence of Tongue Squamous Cell Papilloma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	1/50
Nitrofurantoin	0/50
o-Nitroanisole	0/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	1/50
Rhodamine 6G	0/50
Roxarsone	0/50
Overall Historical Incidence	
Total	6/1,353 (0.4%)
Standard deviation	1.0%
Range	0%-4%

[a] Data as of 31 March 1993

TABLE A4g
Historical Incidence of Oral Cavity Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma or Squamous Cell Papilloma	Squamous Cell Carcinoma	Papilloma, Squamous Cell Papilloma, or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	1/50	0/50	1/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	1/50	0/50	1/50
Polysorbate 80	1/50	0/50	1/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	2/50	0/50	2/50
Overall Historical Incidence			
Total	11/1,353 (0.8%)	0/1,353 (0.0%)	11/1,353 (0.8%)
Standard deviation	1.4%		1.4%
Range	0%-4%		0%-4%

[a] Data as of 31 March 1993 for oral mucosa, tongue, pharynx, tooth, and lip

TABLE A4h
Historical Incidence of Forestomach Squamous Cell Papilloma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	0/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	0/50
Overall Historical Incidence	
Total	3/1,353 (0.2%)
Standard deviation	0.6%
Range	0%-2%

[a] Data as of 31 March 1993

TABLE A4i
Historical Incidence of Large Intestine Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/1,353 (0.0%)	1/1,353 (0.1%)	1/1,353 (0.1%)
Standard deviation		0.4%	0.4%
Range		0%-2%	0%-2%

[a] Data as of 31 March 1993 for cecum, colon, and rectum

TABLE A4j
Historical Incidence of Small Intestine Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute[b]			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	1/50	1/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	1/50	1/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	2/50	2/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/1,353 (0.1%)	6/1,353 (0.4%)	7/1,353 (0.5%)
Standard deviation	0.4%	1.0%	1.1%
Range	0%-2%	0%-4%	0%-4%

[a] Data as of 31 March 1993 for duodenum, ileum, and jejunum
[b] All incidences occurred in the jejunum.

TABLE A4k
Historical Incidence of Mesothelioma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	1/50
C.I. Pigment Red 23	4/50
C.I. Pigment Red 3	3/50
Nitrofurantoin	3/50
o-Nitroanisole	1/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	1/50
Roxarsone	1/50
Overall Historical Incidence	
Total	40/1,353 (3.0%)
Standard deviation	2.4%
Range	0%-8%

[a] Data as of 31 March 1993 for benign, malignant, or unspecified mesothelioma

TABLE A4l
Historical Incidence of Renal Tubule Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	0/49
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	1/50
Overall Historical Incidence	
Total	9/1,350 (0.7%)
Standard deviation	1.5%
Range	0%-6%

[a] Data as of 31 March 1993

TABLE A4m
Historical Incidence of Lung Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls			
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma	Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute				
Benzyl Acetate	1/50	0/50	1/50	0/50
C.I. Pigment Red 23	1/50	0/50	1/50	0/50
C.I. Pigment Red 3	0/50	1/50	1/50	0/50
Nitrofurantoin	0/50	0/50	0/50	0/50
o-Nitroanisole	2/50	1/50	3/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50	0/50
Polysorbate 80	1/50	0/50	1/50	0/50
Rhodamine 6G	2/50	0/50	2/50	0/50
Roxarsone	2/50	0/50	2/50	0/50
Overall Historical Incidence				
Total	32/1,350 (2.4%)	12/1,350 (0.9%)	44/1,350 (3.3%)	0/1,350 (0.0%)
Standard deviation	2.0%	1.2%	1.9%	
Range	0%-6%	0%-4%	0%-8%	

[a] Data as of 31 March 1993

TABLE A4n
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	2/50	1/50	3/50
C.I. Pigment Red 3	1/50	1/50	2/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	1/49	1/49	2/49
p-Nitrobenzoic Acid	0/49	0/49	0/49
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	1/50	1/50	2/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	12/1,343 (0.9%)	11/1,343 (0.8%)	23/1,343 (1.7%)
Standard deviation	1.2%	1.1%	1.6%
Range	0%-4%	0%-4%	0%-6%

[a] Data as of 31 March 1993

TABLE A4o
Historical Incidence of Mononuclear Cell Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	16/50
C.I. Pigment Red 23	28/50
C.I. Pigment Red 3	22/50
Nitrofurantoin	23/50
o-Nitroanisole	26/50
p-Nitrobenzoic Acid	29/50
Polysorbate 80	23/50
Rhodamine 6G	27/50
Roxarsone	27/50
Overall Historical Incidence	
Total	661/1,353 (48.9%)
Standard deviation	8.8%
Range	32%-62%

[a] Data as of 31 March 1993

TABLE A4p
Historical Incidence of Pancreatic Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	1/50
C.I. Pigment Red 23	2/50
C.I. Pigment Red 3	1/50
Nitrofurantoin	2/50
o-Nitroanisole	5/49
p-Nitrobenzoic Acid	2/49
Polysorbate 80	1/50
Rhodamine 6G	2/50
Roxarsone	1/50
Overall Historical Incidence	
Total	24/1,340 (1.8%)
Standard deviation	2.3%
Range	0%-10%

[a] Data as of 31 March 1993

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
Disposition Summary					
Animals initially in study	70	60	60	60	70
3-Month interim evaluation[b]	10				10
15-Month interim evaluation	9	7	9	5	
Early deaths					
Moribund	24	30	36	43	55
Natural deaths	1	3	2	11	5
Survivors					
Terminal sacrifice	26	20	13	1	
Animals examined microscopically	70	60	60	60	70
3-Month Interim Evaluation					
Alimentary System					
Liver	(10)				(10)
Fatty change	4 (40%)				2 (20%)
Hepatodiaphragmatic nodule					3 (30%)
Inflammation, focal					1 (10%)
Mesentery	(1)				
Fat, necrosis	1 (100%)				
Endocrine System					
Adrenal cortex	(10)				(10)
Accessory adrenal cortical nodule					2 (20%)
Thyroid gland	(10)				(10)
Ultimobranchial cyst	2 (20%)				
Genital System					
Preputial gland	(10)				(10)
Degeneration, cystic	9 (90%)				7 (70%)
Inflammation, chronic	1 (10%)				2 (20%)
Prostate	(10)				(10)
Inflammation, suppurative					2 (20%)
Hematopoietic System					
Lymph node					(1)
Mediastinal, hemorrhage					1 (100%)
Urinary System					
Kidney	(10)				(10)
Nephropathy	10 (100%)				3 (30%)
Papilla, degeneration					8 (80%)
Urinary bladder	(10)				(10)
Transitional epithelium, hyperplasia					10 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion
[b] Ten control and ten 20,000 ppm (stop-exposure) rats were evaluated at 3 months.

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
3-Month Interim Evaluation (continued)					
Systems Examined With No Lesions Observed					
Cardiovascular System					
General Body System					
Integumentary System					
Musculoskeletal System					
Nervous System					
Respiratory System					
Special Senses System					
15-Month Interim Evaluation					
Alimentary System					
Intestine large, colon	(9)	(7)	(9)	(5)	
Parasite metazoan	1 (11%)		1 (11%)		
Intestine large, rectum	(9)	(7)	(9)	(5)	
Parasite metazoan	1 (11%)	3 (43%)	2 (22%)	1 (20%)	
Liver	(9)	(7)	(9)	(5)	
Basophilic focus	5 (56%)		3 (33%)		
Degeneration, cystic			1 (11%)		
Eosinophilic focus				1 (20%)	
Fatty change	8 (89%)	6 (86%)	8 (89%)	3 (60%)	
Hepatodiaphragmatic nodule	1 (11%)		1 (11%)		
Hepatodiaphragmatic nodule, multiple		1 (14%)			
Infiltration cellular, mixed cell			2 (22%)		
Inflammation, focal	6 (67%)	3 (43%)	3 (33%)	2 (40%)	
Necrosis, focal	1 (11%)				
Bile duct, hyperplasia	8 (89%)	4 (57%)	6 (67%)	2 (40%)	
Mesentery		(4)	(2)	(1)	
Accessory spleen			1 (50%)		
Fat, necrosis		3 (75%)		1 (100%)	
Pancreas	(9)	(7)	(9)	(5)	
Accessory spleen	1 (11%)				
Atrophy, focal	6 (67%)	4 (57%)	2 (22%)		
Hyperplasia, focal	1 (11%)	1 (14%)	1 (11%)		
Pharynx	(1)				
Palate, epithelium, hyperplasia, focal	1 (100%)				
Stomach, forestomach	(9)	(7)	(9)	(5)	
Hyperplasia		1 (14%)			
Endocrine System					
Adrenal medulla	(9)	(7)	(9)	(5)	
Hyperplasia			2 (22%)		
Pituitary gland	(9)	(7)	(9)	(5)	
Angiectasis				1 (20%)	
Cyst	1 (11%)				
Hemorrhage				1 (20%)	
Pars distalis, focal cellular change	2 (22%)			1 (20%)	
Pars distalis, hyperplasia, focal	1 (11%)	1 (14%)	1 (11%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Endocrine System (continued)					
Thyroid gland	(9)	(7)	(9)	(5)	
Ultimobranchial cyst	1 (11%)				
C-cell, hyperplasia				1 (20%)	
Follicular cell, hyperplasia	2 (22%)				
Genital System					
Epididymis	(9)	(7)	(9)	(5)	
Inflammation, chronic			1 (11%)		
Preputial gland	(9)	(7)	(9)	(5)	
Degeneration, cystic	9 (100%)	7 (100%)	9 (100%)	5 (100%)	
Inflammation, chronic	1 (11%)		1 (11%)		
Prostate	(9)	(7)	(9)	(5)	
Inflammation, suppurative	7 (78%)	6 (86%)	6 (67%)	3 (60%)	
Seminal vesicle	(9)	(7)	(9)	(5)	
Hyperplasia		2 (29%)	5 (56%)	1 (20%)	
Testes	(9)	(7)	(9)	(5)	
Interstitial cell, hyperplasia	1 (11%)	1 (14%)			
Hematopoietic System					
Bone marrow	(9)	(7)	(9)	(5)	
Hypercellularity			1 (11%)		
Lymph node, mesenteric	(9)	(7)	(9)	(5)	
Hyperplasia			1 (11%)		
Spleen	(9)	(7)	(9)	(5)	
Developmental malformation	1 (11%)				
Fibrosis, focal	1 (11%)	1 (14%)			
Musculoskeletal System					
Bone	(9)	(7)	(9)	(5)	
Hyperostosis			1 (11%)	1 (20%)	
Respiratory System					
Nose	(9)	(7)	(9)	(5)	
Fungus			1 (11%)		
Inflammation, suppurative	2 (22%)		1 (11%)		
Urinary System					
Kidney	(9)	(7)	(9)	(5)	
Atrophy, focal				1 (20%)	
Nephropathy	9 (100%)	7 (100%)	9 (100%)	5 (100%)	
Papilla, degeneration			2 (22%)	4 (80%)	
Papilla, epithelium, hyperplasia	1 (11%)		1 (11%)	5 (100%)	
Pelvis, dilatation		1 (14%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
15-Month Interim Evaluation (continued)					
Urinary System (continued)					
Urethra	(1)				
Bulbourethral gland, dilatation	1 (100%)				
Systems Examined With No Lesions Observed					
Cardiovascular System					
General Body System					
Integumentary System					
Nervous System					
Special Senses System					
2-Year Study					
Alimentary System					
Esophagus	(51)	(53)	(51)	(55)	(60)
Epithelium, hyperplasia, focal				1 (2%)	
Intestine large, colon	(51)	(52)	(51)	(54)	(59)
Parasite metazoan	1 (2%)		2 (4%)		2 (3%)
Thrombosis				1 (2%)	
Intestine large, rectum	(51)	(52)	(50)	(53)	(59)
Parasite metazoan	1 (2%)	1 (2%)	3 (6%)	7 (13%)	2 (3%)
Intestine large, cecum	(51)	(52)	(51)	(54)	(59)
Inflammation, chronic	1 (2%)				
Parasite metazoan				1 (2%)	1 (2%)
Ulcer	1 (2%)				
Intestine small, jejunum	(51)	(52)	(51)	(53)	(59)
Diverticulum					2 (3%)
Inflammation, chronic, focal					1 (2%)
Metaplasia, focal, osseous					1 (2%)
Mucosa, hyperplasia				1 (2%)	
Mucosa, hyperplasia, cystic					1 (2%)
Intestine small, ileum	(51)	(52)	(51)	(53)	(59)
Inflammation, chronic, focal	1 (2%)				2 (3%)
Ulcer					1 (2%)
Liver	(51)	(53)	(51)	(55)	(60)
Angiectasis	1 (2%)	2 (4%)	1 (2%)	3 (5%)	3 (5%)
Basophilic focus	27 (53%)	16 (30%)	13 (25%)	10 (18%)	12 (20%)
Clear cell focus	3 (6%)	4 (8%)	1 (2%)	1 (2%)	
Congestion, focal				1 (2%)	1 (2%)
Cyst				2 (4%)	
Degeneration, cystic	9 (18%)	6 (11%)	10 (20%)	5 (9%)	7 (12%)
Developmental malformation					1 (2%)
Eosinophilic focus	3 (6%)	6 (11%)	2 (4%)	1 (2%)	5 (8%)
Fatty change	15 (29%)	19 (36%)	8 (16%)	12 (22%)	17 (28%)
Fibrosis, focal	2 (4%)				
Focal cellular change			1 (2%)		2 (3%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)	3 (5%)	4 (7%)
Hepatodiaphragmatic nodule	4 (8%)	2 (4%)	3 (6%)	4 (7%)	2 (3%)
Hepatodiaphragmatic nodule, multiple	1 (2%)				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Alimentary System (continued)					
Liver (continued)	(51)	(53)	(51)	(55)	(60)
Hyperplasia, focal, histiocytic, lymphoid	1 (2%)				
Infarct			1 (2%)		
Infiltration cellular, mixed cell	10 (20%)	5 (9%)	5 (10%)	8 (15%)	13 (22%)
Inflammation, focal	4 (8%)	5 (9%)	3 (6%)	2 (4%)	9 (15%)
Mixed cell focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis, focal	6 (12%)	1 (2%)	2 (4%)	4 (7%)	2 (3%)
Pigmentation		1 (2%)			
Thrombosis	1 (2%)		1 (2%)	1 (2%)	
Bile duct, dilatation, focal		1 (2%)		1 (2%)	
Bile duct, hyperplasia	47 (92%)	46 (87%)	45 (88%)	41 (75%)	44 (73%)
Biliary tract, cyst	1 (2%)				
Centrilobular, atrophy	20 (39%)	23 (43%)	31 (61%)	26 (47%)	28 (47%)
Centrilobular, congestion		1 (2%)			1 (2%)
Centrilobular, hemorrhage	1 (2%)				
Centrilobular, necrosis		1 (2%)	1 (2%)	4 (7%)	1 (2%)
Hepatocyte, hyperplasia, multifocal	3 (6%)	9 (17%)	10 (20%)	8 (15%)	4 (7%)
Mesentery	(15)	(16)	(19)	(22)	(30)
Inflammation, chronic	1 (7%)	1 (6%)	1 (5%)	2 (9%)	2 (7%)
Fat, necrosis	8 (53%)	6 (38%)	6 (32%)	4 (18%)	7 (23%)
Pancreas	(51)	(53)	(51)	(53)	(59)
Atrophy, diffuse					1 (2%)
Atrophy, focal	27 (53%)	19 (36%)	25 (49%)	26 (49%)	22 (37%)
Autolysis		1 (2%)			
Acinar cell, focal cellular change					1 (2%)
Acinar cell, hyperplasia, focal	3 (6%)	9 (17%)	12 (24%)	14 (26%)	27 (46%)
Duct, dilatation	1 (2%)	1 (2%)	2 (4%)		2 (3%)
Pharynx		(3)	(4)	(5)	(10)
Palate, epithelium, hyperplasia, focal		1 (33%)	1 (25%)	3 (60%)	2 (20%)
Salivary glands	(51)	(52)	(49)	(55)	(60)
Cyst	1 (2%)				
Inflammation, chronic				1 (2%)	
Stomach, forestomach	(51)	(53)	(51)	(55)	(59)
Edema	1 (2%)	1 (2%)	1 (2%)		
Erosion		3 (6%)			1 (2%)
Inflammation, chronic	3 (6%)	9 (17%)	4 (8%)	3 (5%)	3 (5%)
Pigmentation		1 (2%)			
Ulcer	1 (2%)	5 (9%)	4 (8%)	2 (4%)	2 (3%)
Mucosa, cyst		1 (2%)			
Mucosa, hyperplasia	4 (8%)	12 (23%)	6 (12%)	6 (11%)	6 (10%)
Stomach, glandular	(51)	(53)	(51)	(53)	(60)
Edema	1 (2%)	1 (2%)			
Erosion	1 (2%)	1 (2%)		4 (8%)	4 (7%)
Inflammation, chronic		2 (4%)		2 (4%)	
Pigmentation, focal	1 (2%)			1 (2%)	2 (3%)
Mucosa, hyperplasia	1 (2%)				2 (3%)
Tongue		(2)	(5)	(13)	(9)
Epithelium, hyperplasia, focal				4 (31%)	3 (33%)
Tooth	(1)		(1)		(2)
Incisor, dysplasia	1 (100%)				1 (50%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Cardiovascular System					
Blood vessel	(3)	(1)		(2)	(2)
Mesenteric artery, inflammation, chronic				2 (100%)	
Heart	(51)	(53)	(51)	(55)	(60)
Inflammation, chronic, focal				1 (2%)	
Mineralization, focal				1 (2%)	
Thrombosis	1 (2%)	1 (2%)	2 (4%)	2 (4%)	2 (3%)
Endocrine System					
Adrenal cortex	(51)	(53)	(51)	(54)	(60)
Accessory adrenal cortical nodule	7 (14%)	4 (8%)	4 (8%)	4 (7%)	9 (15%)
Angiectasis				1 (2%)	1 (2%)
Atrophy			1 (2%)		
Congestion	3 (6%)		1 (2%)	2 (4%)	1 (2%)
Focal cellular change	7 (14%)	6 (11%)	6 (12%)	14 (26%)	6 (10%)
Hematopoietic cell proliferation				1 (2%)	1 (2%)
Hemorrhage			1 (2%)		
Hyperplasia			1 (2%)		
Necrosis, focal	2 (4%)				1 (2%)
Vacuolization cytoplasmic			1 (2%)	1 (2%)	1 (2%)
Adrenal medulla	(51)	(53)	(51)	(54)	(60)
Angiectasis	1 (2%)				
Hyperplasia	10 (20%)	15 (28%)	11 (22%)	5 (9%)	9 (15%)
Islets, pancreatic	(51)	(53)	(51)	(55)	(59)
Hyperplasia	1 (2%)				1 (2%)
Parathyroid gland	(50)	(51)	(49)	(53)	(58)
Hyperplasia	4 (8%)		1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(51)	(50)	(53)	(57)
Angiectasis		2 (4%)	2 (4%)	2 (4%)	
Cyst	2 (4%)	2 (4%)	1 (2%)	2 (4%)	6 (11%)
Pars distalis, focal cellular change	5 (10%)	3 (6%)	4 (8%)	4 (8%)	6 (11%)
Pars distalis, hyperplasia, focal	4 (8%)	5 (10%)		2 (4%)	5 (9%)
Thyroid gland	(51)	(53)	(51)	(55)	(59)
Ultimobranchial cyst			1 (2%)	3 (5%)	
C-cell, hyperplasia	8 (16%)	11 (21%)	5 (10%)	4 (7%)	15 (25%)
Follicle, dilatation			1 (2%)	3 (5%)	9 (15%)
Follicular cell, hyperplasia	1 (2%)		2 (4%)	5 (9%)	6 (10%)
General Body System					
Tissue NOS	(1)	(2)	(3)	(6)	(8)
Scrotal, inflammation, chronic				1 (17%)	
Genital System					
Coagulating gland		(1)		(2)	(3)
Hyperplasia		1 (100%)		2 (100%)	3 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Genital System (continued)					
Epididymis	(51)	(53)	(51)	(54)	(60)
Granuloma sperm			1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)	
Preputial gland	(51)	(52)	(51)	(55)	(60)
Degeneration, cystic	49 (96%)	52 (100%)	48 (94%)	55 (100%)	57 (95%)
Hyperplasia	2 (4%)	3 (6%)	2 (4%)		
Inflammation, chronic	3 (6%)	3 (6%)	2 (4%)	3 (5%)	6 (10%)
Prostate	(51)	(53)	(51)	(55)	(60)
Inflammation, suppurative	26 (51%)	35 (66%)	28 (55%)	37 (67%)	34 (57%)
Epithelium, hyperplasia, focal	3 (6%)	3 (6%)		1 (2%)	
Seminal vesicle	(51)	(53)	(51)	(55)	(60)
Dilatation				1 (2%)	1 (2%)
Edema	1 (2%)				
Hyperplasia	1 (2%)	6 (11%)	4 (8%)	16 (29%)	33 (55%)
Inflammation, chronic	2 (4%)				
Testes	(51)	(53)	(51)	(55)	(60)
Mineralization, focal				1 (2%)	
Germinal epithelium, degeneration	7 (14%)	7 (13%)	7 (14%)	6 (11%)	4 (7%)
Interstitial cell, hyperplasia	1 (2%)	3 (6%)		1 (2%)	
Hematopoietic System					
Bone marrow	(51)	(53)	(51)	(55)	(60)
Hypercellularity	7 (14%)	7 (13%)	5 (10%)	16 (29%)	18 (30%)
Hyperplasia, focal, histiocytic	1 (2%)				
Metaplasia, osseous				4 (7%)	
Myelofibrosis	2 (4%)		1 (2%)	3 (5%)	2 (3%)
Necrosis, focal					1 (2%)
Lymph node	(25)	(23)	(36)	(27)	(30)
Deep cervical, hyperplasia					1 (3%)
Iliac, hyperplasia		1 (4%)			
Inguinal, hyperplasia	2 (8%)			1 (4%)	
Inguinal, hyperplasia, lymphoid		1 (4%)			
Mediastinal, edema					2 (7%)
Mediastinal, hemorrhage	2 (8%)	3 (13%)	1 (3%)	3 (11%)	3 (10%)
Mediastinal, hyperplasia	1 (4%)			2 (7%)	2 (7%)
Mediastinal, hyperplasia, lymphoid			1 (3%)		1 (3%)
Mediastinal, pigmentation				1 (4%)	3 (10%)
Mediastinal, thrombosis			1 (3%)		
Pancreatic, edema				1 (4%)	
Pancreatic, hemorrhage	1 (4%)	1 (4%)			
Pancreatic, hyperplasia, macrophage		1 (4%)			
Lymph node, mandibular	(49)	(52)	(49)	(55)	(59)
Congestion		1 (2%)	1 (2%)		
Edema	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)	1 (2%)			
Hyperplasia	4 (8%)	2 (4%)	2 (4%)	3 (5%)	10 (17%)
Pigmentation		1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Hematopoietic System (continued)					
Lymph node, mesenteric	(50)	(53)	(51)	(55)	(60)
Edema			1 (2%)	4 (7%)	3 (5%)
Hemorrhage		2 (4%)			
Hyperplasia	1 (2%)			4 (7%)	2 (3%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)		
Spleen	(51)	(53)	(51)	(54)	(60)
Autolysis		1 (2%)			
Congestion				1 (2%)	
Developmental malformation			2 (4%)	1 (2%)	
Fibrosis, focal	15 (29%)	10 (19%)	22 (43%)	24 (44%)	28 (47%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	3 (6%)	8 (15%)	17 (28%)
Necrosis, focal	1 (2%)		2 (4%)		1 (2%)
Pigmentation		1 (2%)			
Thymus	(49)	(53)	(49)	(53)	(57)
Congestion				1 (2%)	
Cyst					1 (2%)
Hemorrhage		1 (2%)			
Integumentary System					
Mammary gland	(48)	(51)	(49)	(48)	(50)
Angiectasis				1 (2%)	
Dilatation	11 (23%)	9 (18%)	11 (22%)	4 (8%)	4 (8%)
Hemorrhage				1 (2%)	
Hyperplasia	3 (6%)	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic				1 (2%)	
Skin	(51)	(53)	(51)	(54)	(59)
Cyst epithelial inclusion		1 (2%)		1 (2%)	2 (3%)
Hemorrhage, focal			1 (2%)		
Hyperkeratosis, focal	1 (2%)	1 (2%)	3 (6%)	2 (4%)	2 (3%)
Inflammation, chronic, focal		1 (2%)	1 (2%)	3 (6%)	3 (5%)
Ulcer				1 (2%)	
Epidermis, hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)	2 (4%)	3 (5%)
Hair follicle, cyst					1 (2%)
Prepuce, inflammation, chronic			1 (2%)		
Sebaceous gland, cyst		1 (2%)			
Sebaceous gland, hyperplasia, focal				1 (2%)	1 (2%)
Subcutaneous tissue, fibrosis	1 (2%)		1 (2%)		1 (2%)
Subcutaneous tissue, inflammation, chronic, focal			1 (2%)	2 (4%)	
Subcutaneous tissue, fat, necrosis				1 (2%)	
Musculoskeletal System					
Bone	(51)	(53)	(51)	(55)	(60)
Hyperostosis	6 (12%)	7 (13%)	3 (6%)	4 (7%)	11 (18%)
Adventitia, calvarium, proliferation connective tissue					1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Musculoskeletal System (continued)					
Skeletal muscle		(3)	(2)	(4)	(4)
Hemorrhage, focal				1 (25%)	
Inflammation, chronic				1 (25%)	
Necrosis, focal				1 (25%)	
Nervous System					
Brain	(51)	(53)	(51)	(55)	(60)
Compression	3 (6%)	7 (13%)	2 (4%)	3 (5%)	3 (5%)
Hemorrhage	3 (6%)	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Respiratory System					
Lung	(51)	(53)	(51)	(55)	(60)
Congestion	1 (2%)		3 (6%)	2 (4%)	
Hemorrhage, focal		1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, diffuse, histiocytic			1 (2%)		
Hyperplasia, focal, histiocytic				1 (2%)	
Inflammation, chronic, focal		2 (4%)	1 (2%)		1 (2%)
Metaplasia, osseous	1 (2%)				1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	4 (8%)	5 (10%)	7 (13%)	14 (23%)
Peribronchial, infiltration cellular, lymphocyte					1 (2%)
Nose	(51)	(53)	(51)	(55)	(60)
Fungus	7 (14%)	3 (6%)	5 (10%)	5 (9%)	5 (8%)
Inflammation, suppurative	10 (20%)	8 (15%)	16 (31%)	11 (20%)	11 (18%)
Mucosa, angiectasis, focal			1 (2%)		
Mucosa, hyperkeratosis, focal			1 (2%)		
Mucosa, hyperplasia, focal			2 (4%)		
Mucosa, metaplasia, focal, squamous			2 (4%)		
Nasolacrimal duct, inflammation, chronic active					1 (2%)
Respiratory epithelium, hyperplasia, focal					1 (2%)
Trachea	(51)	(53)	(51)	(55)	(60)
Glands, dilatation				1 (2%)	
Special Senses System					
Eye	(2)	(1)	(2)		(1)
Atrophy		1 (100%)	1 (50%)		
Cataract	1 (50%)		2 (100%)		
Fibrosis		1 (100%)			
Inflammation, chronic	1 (50%)				
Synechia	1 (50%)		1 (50%)		
Cornea, inflammation, chronic			1 (50%)		
Retina, degeneration		1 (100%)	1 (50%)		
Sclera, mineralization, focal					1 (100%)
Zymbal's gland	(2)	(1)	(5)	(5)	(15)
Dilatation				1 (20%)	1 (7%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm (Stop-Exposure)
2-Year Study (continued)					
Urinary System					
Kidney	(51)	(53)	(51)	(55)	(59)
Atrophy, focal				5 (9%)	
Cyst	2 (4%)			1 (2%)	1 (2%)
Hydronephrosis					1 (2%)
Infarct	1 (2%)				
Inflammation, chronic, suppurative		1 (2%)		1 (2%)	
Nephropathy	51 (100%)	53 (100%)	51 (100%)	53 (96%)	58 (98%)
Cortex, medulla, mineralization, focal				1 (2%)	
Papilla, degeneration		5 (9%)	30 (59%)	29 (53%)	16 (27%)
Papilla, mineralization, focal				2 (4%)	
Papilla, epithelium, hyperplasia	10 (20%)	20 (38%)	25 (49%)	47 (85%)	21 (36%)
Pelvis, dilatation				1 (2%)	1 (2%)
Pelvis, transitional epithelium, hyperplasia				4 (7%)	4 (7%)
Renal tubule, epithelium, hyperplasia, focal			2 (4%)		
Urethra		(1)	(1)	(1)	
Bulbourethral gland, dilatation			1 (100%)	1 (100%)	
Urinary bladder	(51)	(53)	(51)	(55)	(59)
Dilatation		1 (2%)			
Hemorrhage					1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)	2 (3%)
Transitional epithelium, hyperplasia			1 (2%)	3 (5%)	10 (17%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	7	8
Early deaths				
Moribund	14	22	27	41
Natural deaths		2	3	6
Survivors				
Terminal sacrifice	36	27	23	5
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(9)	(9)	(7)	(8)
Pars distalis, adenoma				1 (13%)
Thyroid gland	(10)	(9)	(7)	(8)
C-cell, adenoma			2 (29%)	
Follicular cell, adenoma				1 (13%)
Genital System				
Clitoral gland	(10)	(9)	(7)	(8)
Adenoma			1 (14%)	
Uterus	(10)	(9)	(7)	(8)
Endometrium, polyp stromal			1 (14%)	
Endometrium, polyp stromal, multiple				1 (13%)
Integumentary System				
Mammary gland	(10)	(9)	(7)	(8)
Fibroadenoma	1 (10%)	1 (11%)		1 (13%)
Fibroadenoma, multiple				2 (25%)
Systems Examined With No Neoplasms Observed				
Alimentary System				
Cardiovascular System				
General Body System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study				
Alimentary System				
Esophagus	(50)	(51)	(53)	(52)
Squamous cell papilloma			1 (2%)	10 (19%)
Intestine large, colon	(50)	(51)	(53)	(52)
Polyp adenomatous		1 (2%)		
Intestine large, cecum	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Intestine small, jejunum	(50)	(51)	(53)	(52)
Carcinoma			1 (2%)	
Intestine small, ileum	(50)	(50)	(53)	(52)
Liver	(50)	(51)	(53)	(52)
Carcinoma, multiple, metastatic, islets, pancreatic	1 (2%)			
Mesentery	(6)	(12)	(7)	(6)
Histiocytic sarcoma	1 (17%)			
Pancreas	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Pharynx	(1)	(1)	(1)	(2)
Palate, squamous cell carcinoma		1 (100%)	1 (100%)	
Palate, squamous cell papilloma	1 (100%)			1 (50%)
Salivary glands	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Stomach, forestomach	(50)	(51)	(53)	(52)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Tongue	(1)	(3)	(6)	(6)
Squamous cell carcinoma				1 (17%)
Squamous cell papilloma	1 (100%)	2 (67%)	4 (67%)	4 (67%)
Cardiovascular System				
Heart	(49)	(51)	(53)	(52)
Pericardium, histiocytic sarcoma	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(51)	(53)	(52)
Adenoma			1 (2%)	
Adrenal medulla	(50)	(51)	(53)	(52)
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(51)	(53)	(52)
Adenoma		2 (4%)	1 (2%)	
Carcinoma	1 (2%)			
Pituitary gland	(49)	(51)	(52)	(51)
Pars distalis, adenoma	16 (33%)	24 (47%)	24 (46%)	15 (29%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
C-cell, adenoma	6 (12%)	5 (10%)	5 (9%)	4 (8%)
C-cell, carcinoma	2 (4%)	3 (6%)		
Follicular cell, adenoma			2 (4%)	3 (6%)
Follicular cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(48)	(49)	(49)	(52)
Adenoma	3 (6%)	3 (6%)	6 (12%)	3 (6%)
Carcinoma	1 (2%)			1 (2%)
Histiocytic sarcoma	1 (2%)			
Bilateral, adenoma	1 (2%)			
Ovary	(50)	(51)	(53)	(52)
Granulosa cell tumor benign	1 (2%)			1 (2%)
Uterus	(50)	(51)	(53)	(52)
Endometrium, adenoma			1 (2%)	
Endometrium, carcinoma				1 (2%)
Endometrium, polyp stromal	4 (8%)	8 (16%)	6 (11%)	6 (12%)
Endometrium, polyp stromal, multiple	1 (2%)			
Endometrium, sarcoma stromal		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(51)	(53)	(52)
Lymph node	(16)	(11)	(15)	(19)
Histiocytic sarcoma	1 (6%)			
Inguinal, histiocytic sarcoma	1 (6%)			
Lymph node, mandibular	(49)	(48)	(53)	(50)
Histiocytic sarcoma	1 (2%)			
Lymph node, mesenteric	(50)	(51)	(53)	(52)
Spleen	(50)	(51)	(53)	(52)
Hemangiosarcoma			1 (2%)	1 (2%)
Thymus	(49)	(50)	(51)	(52)
Integumentary System				
Mammary gland	(50)	(51)	(53)	(52)
Adenoma		2 (4%)		
Carcinoma	3 (6%)	4 (8%)	3 (6%)	4 (8%)
Carcinoma, multiple	1 (2%)			
Fibroadenoma	19 (38%)	8 (16%)	6 (11%)	8 (15%)
Fibroadenoma, multiple	6 (12%)	37 (73%)	40 (75%)	37 (71%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin	(50)	(51)	(53)	(52)
Keratoacanthoma			2 (4%)	
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	3 (6%)		1 (2%)	
Trichoepithelioma	1 (2%)			
Subcutaneous tissue, fibroma	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma				2 (4%)
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, lipoma		2 (4%)		
Subcutaneous tissue, sarcoma	1 (2%)			2 (4%)
Musculoskeletal System				
Skeletal muscle	(1)	(1)		(1)
Histiocytic sarcoma	1 (100%)			
Nervous System				
Brain	(49)	(51)	(53)	(52)
Astrocytoma NOS			1 (2%)	1 (2%)
Oligodendroglioma NOS	1 (2%)			
Respiratory System				
Lung	(50)	(51)	(53)	(52)
Alveolar/bronchiolar adenoma				1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)		2 (4%)
Carcinoma, multiple, metastatic, islets, pancreatic	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Mediastinum, histiocytic sarcoma	1 (2%)			
Special Senses System				
Zymbal's gland		(2)	(2)	(1)
Adenoma		1 (50%)		
Carcinoma			2 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(51)	(53)	(52)
Stromal nephroma			1 (2%)	
Renal tubule, adenoma		1 (2%)		
Urinary bladder	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Transitional epithelium, papilloma		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Systemic Lesions				
Multiple organs[b]	(50)	(51)	(53)	(52)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	15 (30%)	13 (25%)	19 (36%)	19 (37%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	1	3	5
2-Year study	45	51	53	52
Total primary neoplasms				
15-Month interim evaluation	1	1	4	6
2-Year study	92	126	131	132
Total animals with benign neoplasms				
15-Month interim evaluation	1	1	3	5
2-Year study	40	49	49	48
Total benign neoplasms				
15-Month interim evaluation	1	1	4	6
2-Year study	65	102	102	96
Total animals with malignant neoplasms				
2-Year study	21	22	27	31
Total malignant neoplasms				
2-Year study	26	24	28	35
Total animals with metastatic neoplasms				
2-Year study	1			
Total metastatic neoplasms				
2-Year study	2			
Total animals with uncertain neoplasms - benign or malignant				
2-Year study	1		1	1
Total uncertain neoplasms				
2-Year study	1		1	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm

Number of Days on Study	4 6 0	4 8 1	5 1 6	6 2 4	6 3 3	6 5 4	6 8 9	6 9 0	6 9 4	6 9 6	6 9 6	7 0 8	7 1 6	7 2 2	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9
Carcass ID Number	3 3 0	3 2	3 1	3 4 1	3 3 3	3 5 4	3 4 9	3 6 1	3 5 3	3 4 6	3 6 7	3 2 3	3 2 9	3 5 8	3 3 4	3 3 5	3 5 1	3 5 2	3 5 5	3 5 6	3 5 7	3 5 9	3 6 0	3 6 2	3 6 3
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple, metastatic, islets, pancreatic										X														
Mesentery		+				+						+												
Histiocytic sarcoma		X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Pharynx																					+			
Palate, squamous cell papilloma																					X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Tongue																								
Squamous cell papilloma																								
Cardiovascular System																								
Blood vessel	+	+	+																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pericardium, histiocytic sarcoma		X																						
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex								X																
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X														
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X			X	X			X				X				X		X			X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
C-cell, adenoma					X		X										X							
C-cell, carcinoma																								
General Body System																								
None																								

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	3 6 4	3 6 5	3 6 6	3 6 8	3 6 9	3 7 0	3 2 1	3 2 2	3 2 4	3 2 5	3 2 6	3 2 7	3 2 8	3 3 6	3 3 7	3 3 8	3 3 9	3 4 0	3 4 2	3 4 3	3 4 4	3 4 5	3 4 7	3 4 8	3 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, multiple, metastatic, islets, pancreatic																										1
Mesentery															+						+	+				6
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Pharynx																										1
Palate, squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Tongue					+																					1
Squamous cell papilloma					X																					1
Cardiovascular System																										
Blood vessel																										3
Heart	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pericardium, histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X		X				X						X					X					X			16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
C-cell, adenoma		X																X							X	6
C-cell, carcinoma							X				X															2
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	4 6 0	4 8 1	5 1 6	6 2 4	6 3 3	6 5 4	6 8 9	6 9 0	6 9 4	6 9 6	6 9 6	7 0 8	7 1 6	7 2 2	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9
Carcass ID Number	3 3 0	3 3 2	3 3 1	3 4 1	3 3 3	3 5 4	3 4 9	3 6 1	3 5 3	3 4 6	3 6 7	3 2 3	3 2 9	3 5 8	3 3 4	3 3 5	3 5 1	3 5 2	3 5 5	3 5 6	3 5 7	3 5 9	3 6 0	3 6 2	3 6 3
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X									X
Carcinoma																				X				
Histiocytic sarcoma		X																						
Bilateral, adenoma	X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																						X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal								X										X						
Endometrium, polyp stromal, multiple																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+			+	+	+	+						+				+		
Histiocytic sarcoma		X																						
Inguinal, histiocytic sarcoma		X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal						+			+	+	+	+												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X	X											
Carcinoma, multiple				X																				
Fibroadenoma			X						X	X			X							X	X	X		
Fibroadenoma, multiple											X							X					X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma								X										X						
Trichoepithelioma																								
Subcutaneous tissue, fibroma																								
Subcutaneous tissue, histiocytic sarcoma		X																						
Subcutaneous tissue, sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																						
Histiocytic sarcoma		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma NOS														X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	3 6 4	3 6 5	3 6 6	3 6 8	3 6 9	3 7 0	3 2 1	3 2 2	3 2 4	3 2 5	3 2 6	3 2 7	3 2 8	3 3 6	3 3 7	3 3 8	3 3 9	3 4 0	3 4 2	3 4 3	3 4 4	3 4 5	3 4 7	3 4 8	3 5 0	Total Tissues/ Tumors
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Adenoma															X										3
Carcinoma																									1
Histiocytic sarcoma																									1
Bilateral, adenoma																									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal							X							X											4
Endometrium, polyp stromal, multiple				X																					1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+				+	+			+							+			+			+	16
Histiocytic sarcoma																									1
Inguinal, histiocytic sarcoma																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Histiocytic sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal		+	+				+	+										+						+	11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X														3
Carcinoma, multiple																									1
Fibroadenoma			X	X				X		X	X			X	X			X	X	X			X		X	19
Fibroadenoma, multiple		X																				X			6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																						3
Trichoepithelioma																		X							1
Subcutaneous tissue, fibroma																X									1
Subcutaneous tissue, histiocytic sarcoma																									1
Subcutaneous tissue, sarcoma								X																	1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									1
Histiocytic sarcoma																									1
Nervous System																									
Brain	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oligodendroglioma NOS																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	4 6 0	4 8 1	5 1 6	6 2 4	6 3 3	6 5 4	6 8 9	6 9 0	6 9 4	6 9 6	6 9 6	7 0 8	7 1 6	7 2 2	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9
Carcass ID Number	3 3 0	3 2	3 1	3 1	3 3	3 4	3 9	3 1	3 3	3 6	3 7	3 3	3 9	3 8	3 4	3 5	3 1	3 2	3 5	3 6	3 7	3 9	3 0	3 2	3 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, multiple, metastatic, islets, pancreatic										X															
Histiocytic sarcoma		X																							
Mediastinum, histiocytic sarcoma		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+						+								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Leukemia mononuclear						X				X	X	X	X	X				X			X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	3 6 4	3 6 5	3 6 6	3 6 8	3 6 9	3 7 0	3 2 1	3 2 2	3 2 4	3 2 5	3 2 6	3 2 7	3 2 8	3 3 6	3 3 7	3 3 8	3 3 9	3 4 0	3 4 2	3 4 3	3 4 4	3 4 5	3 4 7	3 4 8	3 5 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, multiple, metastatic, islets, pancreatic																										1
Histiocytic sarcoma																										1
Mediastinum, histiocytic sarcoma																										1
Nose	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+																				3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear				X				X										X			X	X		X		15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm

Number of Days on Study	4 0 4	4 6 0	5 0 9	6 0 9	6 1 9	6 4 5	6 5 6	6 7 6	6 8 0	6 8 3	6 8 4	6 8 4	6 9 5	6 9 5	6 9 7	7 0 1	7 0 4	7 0 9	7 1 9	7 2 2	7 2 3	7 2 3	7 2 5	7 2 5	7 3 8
Carcass ID Number	4 2 5	3 8 3	4 2 9	4 0 9	4 1 0	3 9 4	3 8 6	4 1 2	3 9 2	3 9 1	4 0 7	4 2 4	3 8 4	4 1 9	4 0 5	4 1 7	3 2 3	3 9 8	3 9 7	4 1 5	3 8 8	4 0 4	3 8 5	3 8 7	4 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous			X																						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+	+			+	+				+								+		+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																					+				
Palate, squamous cell carcinoma																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel										+															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X			X	X					X		X	X				X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X						X													
C-cell, carcinoma																				X					
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal											X			X						X					
Endometrium, sarcoma stromal																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	4 2 2	4 3 0	4 3 1	3 8 1	3 8 2	3 8 9	3 9 0	3 9 3	3 9 5	3 9 6	3 9 9	4 0 0	4 0 1	4 0 2	4 0 3	4 0 6	4 0 8	4 1 1	4 1 3	4 1 4	4 1 6	4 1 8	4 2 0	4 2 6	4 2 7	4 2 8	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp adenomatous																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Mesentery		+						+			+			+			+										12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pharynx																											1
Palate, squamous cell carcinoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tongue			+											+			+										3
Squamous cell papilloma			X														X										2
Cardiovascular System																											
Blood vessel																											1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign																							X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																										X	2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma				X	X	X	X	X				X	X			X		X		X	X	X	X		X	X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma				X					X							X											5
C-cell, carcinoma																				X						X	3
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X							X			X										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endometrium, polyp stromal	X	X											X					X					X				8
Endometrium, sarcoma stromal			X																								1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	4	4	5	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
	0	6	0	0	1	4	5	7	8	8	8	8	9	9	9	0	0	0	1	2	2	2	2	3
	4	0	9	9	9	5	6	6	0	3	4	4	5	5	7	1	4	9	9	2	3	3	5	8
Carcass ID Number	4	3	4	4	4	3	3	4	3	3	4	4	3	4	4	4	4	3	3	4	3	4	3	4
	2	8	2	0	1	9	8	1	9	9	0	2	8	1	0	1	2	9	9	1	8	0	8	2
	5	3	9	9	0	4	6	2	2	1	7	4	4	9	5	7	3	8	7	5	8	4	5	1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+				+	+			+										+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma	X																							
Fibroadenoma		X		X					X										X					X
Fibroadenoma, multiple						X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																	X							
Subcutaneous tissue, fibroma										X													X	X
Subcutaneous tissue, lipoma										X														X
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Lacrimal gland														+										
Zymbal's gland																								M
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X	X		X	X		X					X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 2,500 ppm (continued)

Number of Days on Study	7 3 3 8	7 3 3 8	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	7 3 3 9	
Carcass ID Number	4 2 2	4 3 0	4 3 1	3 8 1	3 8 2	3 8 9	3 9 0	3 9 3	3 9 5	3 9 6	3 9 9	4 0 0	4 0 1	4 0 2	4 0 3	4 0 6	4 0 8	4 1 1	4 1 3	4 1 4	4 1 6	4 1 8	4 2 0	4 2 6	4 2 7	4 2 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node					+		+	+						+	+											11
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mediastinal					+																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma					X		X																			2
Carcinoma													X		X									X		4
Fibroadenoma							X				X								X							8
Fibroadenoma, multiple	X	X	X	X	X	X		X		X		X	X	X		X	X	X		X	X	X	X	X	X	37
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma																X										4
Subcutaneous tissue, lipoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle										+																1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																						+				1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye																+										1
Lacrimal gland			+																							2
Zymbal's gland			+										+													2
Adenoma													X													1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, adenoma								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Transitional epithelium, papilloma																X										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear					X		X			X										X						13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm

Number of Days on Study	3 8 8	4 0 9	4 3 2	4 8 1	5 0 8	5 6 5	5 7 6	5 8 5	6 1 0	6 2 7	6 3 1	6 3 2	6 3 3	6 3 0	6 6 2	6 6 0	6 7 4	6 7 0	6 7 3	6 8 2	6 8 3	6 9 4	6 9 5	6 9 5	6 9 6	6 9 7	6 9 7
Carcass ID Number	5 0 0	4 8 8	4 8 9	4 5 7	4 6 0	4 5 2	4 4 8	4 6 8	4 4 2	4 7 5	4 4 7	4 8 0	4 8 7	4 5 9	4 6 3	4 6 4	4 6 7	4 9 0	4 6 2	4 9 1	4 5 0	4 6 6	4 8 4	4 5 3	4 4 6	4 6 7	4 5 8
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																											
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+										+		+								+		+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx															+												
Palate, squamous cell carcinoma															X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+						+		+									
Squamous cell papilloma										X						X		X									
Tooth			+																								
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																											
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X		X	X			X					X			X	X	X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X				X																			
Follicular cell, adenoma					X																						
General Body System																											
Tissue NOS															+												
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X															X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, adenoma																											
Endometrium, polyp stromal																		X			X						X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	7 0 4	7 1 9	7 2 6	7 2 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	4 4 8 5	4 4 8 1	4 4 5 1	4 4 7 2	4 4 4 1	4 4 4 3	4 4 4 4	4 4 4 5	4 4 4 9	4 4 5 4	4 4 5 5	4 4 5 6	4 4 6 1	4 4 6 5	4 4 6 9	4 4 7 0	4 4 7 1	4 4 7 3	4 4 7 4	4 4 7 6	4 4 7 7	4 4 7 8	4 4 7 9	4 4 8 2	4 4 8 3	4 4 8 6	4 4 9 2	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell papilloma																								X				1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery			+																+									7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pharynx																												1
Palate, squamous cell carcinoma																												1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue										+					+										+			6
Squamous cell papilloma										X																		4
Tooth																											+	2
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																						X						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma benign																			X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																												1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma					X	X			X	X	X	X	X		X	X							X		X	X	X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma									X	X				X														5
Follicular cell, adenoma																										X		2
General Body System																												
Tissue NOS																												1
Genital System																												
Clitoral gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X				X				X					X								6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endometrium, adenoma																			X									1
Endometrium, polyp stromal					X				X			X																6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	3 8 8	4 0 9	4 3 2	4 8 1	5 0 8	5 6 5	5 7 6	5 8 5	6 1 0	6 2 7	6 3 1	6 3 2	6 3 3	6 6 0	6 6 2	6 7 0	6 7 0	6 7 3	6 8 2	6 8 3	6 9 4	6 9 5	6 9 5	6 9 6	6 9 7	6 9 7
Carcass ID Number	5 0 0	4 8 0	4 8 9	4 5 7	4 6 0	4 5 2	4 4 8	4 6 8	4 4 2	4 7 5	4 4 7	4 8 0	4 8 7	4 5 9	4 6 3	4 6 4	4 7 7	4 9 0	4 6 2	4 9 1	4 5 0	4 6 6	4 8 4	4 5 3	4 4 6	4 5 8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+			+			+	+				+		+		+			+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal		+	+		+			+																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X													X							X					
Fibroadenoma							X	X		X	X			X												
Fibroadenoma, multiple						X			X				X		X	X	X	X	X	X	X	X	X	X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X						
Squamous cell papilloma																				X						
Subcutaneous tissue, fibroma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS											X															
Spinal cord																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye															+											
Harderian gland															+											
Zymbal's gland				+																						
Carcinoma				X																						
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stromal nephroma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X				X	X			X	X			X			X	X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 5,000 ppm (continued)

Number of Days on Study	7 0 4	7 1 9	7 2 6	7 2 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	4 8 5	4 8 1	4 5 1	4 7 2	4 4 1	4 4 3	4 4 4	4 4 5	4 4 9	4 5 4	4 5 5	4 5 6	4 6 1	4 6 5	4 6 9	4 7 0	4 7 1	4 7 3	4 7 4	4 7 6	4 7 7	4 7 8	4 7 9	4 8 2	4 8 3	4 8 6	4 9 2	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node		+							+																			15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mediastinal									+																			5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangiosarcoma																												1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma																												3
Fibroadenoma																	X											6
Fibroadenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	40
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma												X																2
Squamous cell papilloma																												1
Subcutaneous tissue, fibroma																	X											1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma NOS																												1
Spinal cord				+																								1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																												
Eye											+														+			3
Harderian gland																												1
Zymbal's gland										+																		2
Carcinoma										X																		2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stromal nephroma													X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X	X		X			X	X		X												X					19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm

Number of Days on Study	3 6 9	4 3 2	4 6 0	4 7 4	5 0 9	5 1 6	5 2 3	5 4 0	5 5 1	5 7 4	5 7 7	5 8 5	5 8 5	5 9 2	5 9 2	5 9 4	5 9 8	6 1 0	6 1 0	6 1 9	6 2 5	6 2 5	6 2 7	6 3 0	6 3 1
Carcass ID Number	5 0 3	5 0 8	5 3 5	5 4 9	5 4 6	5 3 6	5 4 3	5 2 3	5 0 1	5 2 0	5 5 1	5 0 5	5 2 4	5 3 8	5 4 4	5 4 7	5 2 2	5 1 4	5 5 2	5 1 3	5 0 6	5 0 9	5 2 7	5 0 4	5 0 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma				X																			X	X	X
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+							+			+				+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue											+													+	+
Squamous cell carcinoma																									X
Squamous cell papilloma											X														
Cardiovascular System																									
Blood vessel							+	+	+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X	X				X				X	X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Carcinoma				X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, carcinoma																									
Endometrium, polyp stromal	X											X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	6 3 1	6 3 4	6 4 5	6 5 9	6 6 0	6 6 0	6 7 0	6 8 0	6 8 2	6 8 2	6 8 3	6 8 3	6 8 4	6 8 4	6 8 4	6 8 9	6 9 4	6 9 4	7 0 9	7 2 2	7 2 5	7 2 5	7 2 6	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	5 1 1 6	5 1 8	5 1 0	5 4 7	5 2 6	5 3 4	5 2 5	5 2 1	5 1 1	5 1 3	5 3 7	5 4 0	5 1 2	5 4 8	5 0 7	5 3 2	5 4 2	5 4 5	5 2 9	5 1 9	5 5 0	5 4 1	5 1 5	5 2 8	5 3 0	5 3 1	5 3 9	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma					X				X			X			X	X				X									10
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesentery				+					+																				6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pharynx		+																								+			2
Palate, squamous cell papilloma																										X			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma																										X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tongue		+										+													+				6
Squamous cell carcinoma																													1
Squamous cell papilloma		X										X													X				4
Cardiovascular System																													
Blood vessel																													3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma					X	X	X		X				X							X	X			X					15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma								X																X	X				4
Follicular cell, adenoma															X							X		X				3
Follicular cell, carcinoma																										X			1
General Body System																													
None																													
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma										X							X												3
Carcinoma																													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Granulosa cell tumor benign																									X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endometrium, carcinoma															X														1
Endometrium, polyp stromal	X							X													X						X		6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6
	6	3	6	7	0	1	2	4	5	7	7	8	8	9	9	9	1	1	1	2	2	2	3
	9	2	0	4	9	6	3	0	1	4	7	5	5	2	2	4	8	0	0	9	5	7	0
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	0	0	3	4	4	3	4	2	0	2	5	0	2	3	4	1	2	1	5	1	0	0	2
	3	8	5	9	6	6	3	3	1	0	1	5	4	8	4	7	2	4	2	3	6	9	7
Hematopoietic System																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+			+	+		+	+						+					+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal		+						+		+	+						+					+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																							
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X			X		X																
Fibroadenoma			X		X								X		X			X				X	
Fibroadenoma, multiple				X					X		X			X		X	X		X	X	X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma											X												
Subcutaneous tissue, fibrosarcoma						X																	
Subcutaneous tissue, sarcoma												X											
Musculoskeletal System																							
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							
Nervous System																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																							
Peripheral nerve								+	+														
Respiratory System																							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							
Alveolar/bronchiolar carcinoma																X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																							
Zymbal's gland											+												
Carcinoma											X												
Urinary System																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X	X						X				X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 10,000 ppm (continued)

Number of Days on Study	6 3 1	6 3 4	6 4 5	6 5 9	6 6 0	6 6 0	6 7 0	6 8 0	6 8 2	6 8 2	6 8 3	6 8 3	6 8 4	6 8 4	6 8 9	6 9 4	6 9 4	7 0 9	7 2 2	7 2 5	7 2 5	7 2 6	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	5 1 1 6	5 1 8	5 1 0	5 4 7	5 2 6	5 3 4	5 2 5	5 2 1	5 1 1	5 1 3	5 3 7	5 4 0	5 1 2	5 4 8	5 5 7	5 3 2	5 4 2	5 4 5	5 2 9	5 1 9	5 5 0	5 4 1	5 1 5	5 2 8	5 3 0	5 3 1	5 3 9	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node			+	+	+				+	+							+	+		+					+		19
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mediastinal				+					+	+							+	+		+							13
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma							X																				4
Fibroadenoma																					X			X			8
Fibroadenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	37
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Subcutaneous tissue, fibroma																										X	2
Subcutaneous tissue, fibrosarcoma																					X						2
Subcutaneous tissue, sarcoma		X																									2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skeletal muscle		+																									1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Astrocytoma NOS																			X								1
Peripheral nerve																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma												X															1
Alveolar/bronchiolar carcinoma												X															2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																											
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leukemia mononuclear			X	X	X				X	X		X	X	X				X		X					X		X	19

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Clitoral Gland: Adenoma				
Overall rate[a]	4/48 (8%)	3/49 (6%)	6/49 (12%)	3/52 (6%)
Adjusted rate[b]	10.6%	11.1%	23.1%	15.6%
Terminal rate[c]	3/34 (9%)	3/27 (11%)	4/21 (19%)	0/5 (0%)
First incidence (days)	460	738 (T)	565	610
Life table test[d]	P=0.068	P=0.607N	P=0.176	P=0.272
Logistic regression test[d]	P=0.575N	P=0.482N	P=0.393	P=0.433N
Cochran-Armitage test[d]	P=0.452N			
Fisher exact test[d]		P=0.488N	P=0.383	P=0.455N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	5/48 (10%)	3/49 (6%)	6/49 (12%)	4/52 (8%)
Adjusted rate	13.5%	11.1%	23.1%	17.4%
Terminal rate	4/34 (12%)	3/27 (11%)	4/21 (19%)	0/5 (0%)
First incidence (days)	460	738 (T)	565	474
Life table test	P=0.050	P=0.471N	P=0.258	P=0.202
Logistic regression test	P=0.524N	P=0.342N	P=0.512	P=0.333N
Cochran-Armitage test	P=0.482N			
Fisher exact test		P=0.346N	P=0.515	P=0.449N
Esophagus: Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/51 (0%)	1/53 (2%)	10/52 (19%)
Adjusted rate	0.0%	0.0%	4.3%	42.4%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	0/5 (0%)
First incidence (days)	—[e]	—	738 (T)	474
Life table test	P<0.001	—	P=0.411	P<0.001
Logistic regression test	P<0.001	—	P=0.411	P=0.002
Cochran-Armitage test	P<0.001			
Fisher exact test		—	P=0.515	P<0.001
Mammary Gland: Fibroadenoma				
Overall rate	25/50 (50%)	45/51 (88%)	46/53 (87%)	45/52 (87%)
Adjusted rate	60.7%	95.7%	97.9%	100.0%
Terminal rate	20/36 (56%)	25/27 (93%)	22/23 (96%)	5/5 (100%)
First incidence (days)	516	460	565	460
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Mammary Gland: Carcinoma				
Overall rate	4/50 (8%)	4/51 (8%)	3/53 (6%)	4/52 (8%)
Adjusted rate	9.7%	12.9%	7.2%	10.6%
Terminal rate	1/36 (3%)	3/27 (11%)	0/23 (0%)	0/5 (0%)
First incidence (days)	624	404	388	432
Life table test	P=0.196	P=0.541	P=0.617N	P=0.277
Logistic regression test	P=0.211N	P=0.603N	P=0.341N	P=0.313N
Cochran-Armitage test	P=0.531N			
Fisher exact test		P=0.631N	P=0.467N	P=0.620N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	25/50 (50%)	45/51 (88%)	46/53 (87%)	45/52 (87%)
Adjusted rate	60.7%	95.7%	97.9%	100.0%
Terminal rate	20/36 (56%)	25/27 (93%)	22/23 (96%)	5/5 (100%)
First incidence (days)	516	460	565	460
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Mammary Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	6/51 (12%)	3/53 (6%)	4/52 (8%)
Adjusted rate	9.7%	20.1%	7.2%	10.6%
Terminal rate	1/36 (3%)	5/27 (19%)	0/23 (0%)	0/5 (0%)
First incidence (days)	624	404	388	432
Life table test	P=0.208	P=0.257	P=0.617N	P=0.277
Logistic regression test	P=0.168N	P=0.403	P=0.341N	P=0.313N
Cochran-Armitage test	P=0.424N			
Fisher exact test		P=0.383	P=0.467N	P=0.620N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	27/50 (54%)	47/51 (92%)	47/53 (89%)	47/52 (90%)
Adjusted rate	62.5%	97.9%	97.9%	100.0%
Terminal rate	20/36 (56%)	26/27 (96%)	22/23 (96%)	5/5 (100%)
First incidence (days)	516	404	388	432
Life table test	P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P<0.001	P<0.001
Oral Cavity (Pharynx or Tongue): Squamous Cell Papilloma				
Overall rate	2/50 (4%)	2/51 (4%)	4/53 (8%)	5/52 (10%)
Adjusted rate	5.6%	7.4%	11.5%	47.0%
Terminal rate	2/36 (6%)	2/27 (7%)	1/23 (4%)	2/5 (40%)
First incidence (days)	738 (T)	738 (T)	627	577
Life table test	P=0.001	P=0.588	P=0.219	P=0.003
Logistic regression test	P=0.054	P=0.588	P=0.348	P=0.094
Cochran-Armitage test	P=0.123			
Fisher exact test		P=0.684N	P=0.367	P=0.235
Oral Cavity (Pharynx or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	2/50 (4%)	3/51 (6%)	5/53 (9%)	6/52 (12%)
Adjusted rate	5.6%	10.4%	13.8%	48.9%
Terminal rate	2/36 (6%)	2/27 (7%)	1/23 (4%)	2/5 (40%)
First incidence (days)	738 (T)	723	627	577
Life table test	P<0.001	P=0.383	P=0.131	P=0.001
Logistic regression test	P=0.042	P=0.424	P=0.236	P=0.064
Cochran-Armitage test	P=0.089			
Fisher exact test		P=0.509	P=0.243	P=0.148

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/49 (33%)	24/51 (47%)	24/52 (46%)	15/51 (29%)
Adjusted rate	38.8%	65.0%	69.8%	60.2%
Terminal rate	11/35 (31%)	15/27 (56%)	13/22 (59%)	1/5 (20%)
First incidence (days)	460	619	481	460
Life table test	P<0.001	P=0.023	P=0.006	P=0.003
Logistic regression test	P=0.511N	P=0.094	P=0.090	P=0.458N
Cochran-Armitage test	P=0.256N			
Fisher exact test		P=0.103	P=0.118	P=0.447N
Skin: Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/51 (0%)	1/53 (2%)	0/52 (0%)
Adjusted rate	7.8%	0.0%	2.9%	0.0%
Terminal rate	2/36 (6%)	0/27 (0%)	0/23 (0%)	0/5 (0%)
First incidence (days)	690	—	683	—
Life table test	P=0.250N	P=0.165N	P=0.439N	P=0.525N
Logistic regression test	P=0.118N	P=0.124N	P=0.325N	P=0.289N
Cochran-Armitage test	P=0.081N			
Fisher exact test		P=0.118N	P=0.287N	P=0.114N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	1/51 (2%)	1/53 (2%)	0/52 (0%)
Adjusted rate	7.8%	2.9%	2.9%	0.0%
Terminal rate	2/36 (6%)	0/27 (0%)	0/23 (0%)	0/5 (0%)
First incidence (days)	690	704	683	—
Life table test	P=0.253N	P=0.379N	P=0.439N	P=0.525N
Logistic regression test	P=0.103N	P=0.308N	P=0.325N	P=0.289N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.301N	P=0.287N	P=0.114N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Squamous Cell Carcinoma				
Overall rate	4/50 (8%)	1/51 (2%)	2/53 (4%)	0/52 (0%)
Adjusted rate	10.5%	2.9%	7.2%	0.0%
Terminal rate	3/36 (8%)	0/27 (0%)	1/23 (4%)	0/5 (0%)
First incidence (days)	690	704	683	—
Life table test	P=0.277N	P=0.252N	P=0.524N	P=0.452N
Logistic regression test	P=0.112N	P=0.186N	P=0.401N	P=0.232N
Cochran-Armitage test	P=0.048N			
Fisher exact test		P=0.175N	P=0.312N	P=0.054N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	4/51 (8%)	1/53 (2%)	2/52 (4%)
Adjusted rate	2.8%	12.7%	4.3%	21.9%
Terminal rate	1/36 (3%)	2/27 (7%)	1/23 (4%)	1/5 (20%)
First incidence (days)	738 (T)	683	738 (T)	577
Life table test	P=0.122	P=0.122	P=0.659	P=0.123
Logistic regression test	P=0.406	P=0.167	P=0.659	P=0.443
Cochran-Armitage test	P=0.580N			
Fisher exact test		P=0.187	P=0.738N	P=0.515

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	0/51 (0%)	0/53 (0%)	4/52 (8%)
Adjusted rate	2.8%	0.0%	0.0%	19.7%
Terminal rate	1/36 (3%)	0/27 (0%)	0/23 (0%)	0/5 (0%)
First incidence (days)	738 (T)	—	—	516
Life table test	P=0.003	P=0.557N	P=0.589N	P=0.030
Logistic regression test	P=0.053	P=0.557N	P=0.589N	P=0.274
Cochran-Armitage test	P=0.030			
Fisher exact test		P=0.495N	P=0.485N	P=0.194
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	2/50 (4%)	4/51 (8%)	1/53 (2%)	6/52 (12%)
Adjusted rate	5.6%	12.7%	4.3%	37.3%
Terminal rate	2/36 (6%)	2/27 (7%)	1/23 (4%)	1/5 (20%)
First incidence (days)	738 (T)	683	738 (T)	516
Life table test	P=0.002	P=0.238	P=0.655N	P=0.004
Logistic regression test	P=0.093	P=0.311	P=0.655N	P=0.171
Cochran-Armitage test	P=0.123			
Fisher exact test		P=0.348	P=0.478N	P=0.148
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	5/51 (10%)	5/53 (9%)	4/52 (8%)
Adjusted rate	15.0%	15.2%	16.6%	44.5%
Terminal rate	4/36 (11%)	3/27 (11%)	3/23 (13%)	2/5 (40%)
First incidence (days)	633	645	481	594
Life table test	P=0.123	P=0.613	P=0.532	P=0.117
Logistic regression test	P=0.394N	P=0.493N	P=0.435N	P=0.646
Cochran-Armitage test	P=0.292N			
Fisher exact test		P=0.486N	P=0.459N	P=0.346N
Thyroid Gland (C-cell): Carcinoma				
Overall rate	2/50 (4%)	3/51 (6%)	0/53 (0%)	0/52 (0%)
Adjusted rate	5.6%	10.3%	0.0%	0.0%
Terminal rate	2/36 (6%)	2/27 (7%)	0/23 (0%)	0/5 (0%)
First incidence (days)	738 (T)	722	—	—
Life table test	P=0.304N	P=0.384	P=0.341N	P=0.712N
Logistic regression test	P=0.252N	P=0.426	P=0.341N	P=0.712N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.509	P=0.233N	P=0.238N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	8/51 (16%)	5/53 (9%)	4/52 (8%)
Adjusted rate	20.3%	24.7%	16.6%	44.5%
Terminal rate	6/36 (17%)	5/27 (19%)	3/23 (13%)	2/5 (40%)
First incidence (days)	633	645	481	594
Life table test	P=0.252	P=0.423	P=0.522N	P=0.173
Logistic regression test	P=0.200N	P=0.599	P=0.241N	P=0.517N
Cochran-Armitage test	P=0.089N			
Fisher exact test		P=0.590N	P=0.240N	P=0.160N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/50 (0%)	0/51 (0%)	2/53 (4%)	3/52 (6%)
Adjusted rate	0.0%	0.0%	6.3%	35.4%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	1/5 (20%)
First incidence (days)	—	—	508	689
Life table test	P<0.001	—	P=0.193	P=0.001
Logistic regression test	P=0.021	—	P=0.320	P=0.012
Cochran-Armitage test	P=0.030			
Fisher exact test		—	P=0.262	P=0.129
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/51 (0%)	2/53 (4%)	4/52 (8%)
Adjusted rate	0.0%	0.0%	6.3%	51.5%
Terminal rate	0/36 (0%)	0/27 (0%)	1/23 (4%)	2/5 (40%)
First incidence (days)	—	—	508	689
Life table test	P<0.001	—	P=0.193	P<0.001
Logistic regression test	P=0.003	—	P=0.320	P=0.001
Cochran-Armitage test	P=0.009			
Fisher exact test		—	P=0.262	P=0.064
Tongue: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	2/51 (4%)	4/53 (8%)	4/52 (8%)
Adjusted rate	2.8%	7.4%	11.5%	29.3%
Terminal rate	1/36 (3%)	2/27 (7%)	1/23 (4%)	1/5 (20%)
First incidence (days)	738 (T)	738 (T)	627	577
Life table test	P=0.003	P=0.400	P=0.116	P=0.012
Logistic regression test	P=0.081	P=0.400	P=0.198	P=0.144
Cochran-Armitage test	P=0.124			
Fisher exact test		P=0.508	P=0.200	P=0.194
Tongue: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	2/51 (4%)	4/53 (8%)	5/52 (10%)
Adjusted rate	2.8%	7.4%	11.5%	31.8%
Terminal rate	1/36 (3%)	2/27 (7%)	1/23 (4%)	1/5 (20%)
First incidence (days)	738 (T)	738 (T)	627	577
Life table test	P<0.001	P=0.400	P=0.116	P=0.005
Logistic regression test	P=0.041	P=0.400	P=0.198	P=0.091
Cochran-Armitage test	P=0.059			
Fisher exact test		P=0.508	P=0.200	P=0.112
Uterus: Stromal Polyp				
Overall rate	5/50 (10%)	8/51 (16%)	6/53 (11%)	6/52 (12%)
Adjusted rate	13.2%	25.0%	20.7%	38.6%
Terminal rate	4/36 (11%)	5/27 (19%)	3/23 (13%)	1/5 (20%)
First incidence (days)	690	684	670	369
Life table test	P=0.008	P=0.155	P=0.260	P=0.016
Logistic regression test	P=0.372	P=0.246	P=0.415	P=0.528
Cochran-Armitage test	P=0.541N			
Fisher exact test		P=0.290	P=0.541	P=0.528

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	9/51 (18%)	6/53 (11%)	6/52 (12%)
Adjusted rate	13.2%	28.4%	20.7%	38.6%
Terminal rate	4/36 (11%)	6/27 (22%)	3/23 (13%)	1/5 (20%)
First incidence (days)	690	684	670	369
Life table test	P=0.009	P=0.095	P=0.260	P=0.016
Logistic regression test	P=0.392	P=0.164	P=0.415	P=0.528
Cochran-Armitage test	P=0.496N			
Fisher exact test		P=0.206	P=0.541	P=0.528
All Organs: Mononuclear Cell Leukemia				
Overall rate	15/50 (30%)	13/51 (25%)	19/53 (36%)	19/52 (37%)
Adjusted rate	35.6%	32.5%	47.4%	75.2%
Terminal rate	9/36 (25%)	4/27 (15%)	5/23 (22%)	2/5 (40%)
First incidence (days)	654	609	409	540
Life table test	P<0.001	P=0.546	P=0.067	P<0.001
Logistic regression test	P=0.439	P=0.403N	P=0.391	P=0.091
Cochran-Armitage test	P=0.180			
Fisher exact test		P=0.388N	P=0.337	P=0.312
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	49/51 (96%)	49/53 (92%)	48/52 (92%)
Adjusted rate	85.0%	98.0%	100.0%	100.0%
Terminal rate	29/36 (81%)	26/27 (96%)	23/23 (100%)	5/5 (100%)
First incidence (days)	460	460	481	369
Life table test	P<0.001	P=0.004	P<0.001	P<0.001
Logistic regression test	P=0.005	P=0.008	P=0.008	P=0.011
Cochran-Armitage test	P=0.079			
Fisher exact test		P=0.013	P=0.028	P=0.064
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	22/51 (43%)	27/53 (51%)	31/52 (60%)
Adjusted rate	46.4%	54.1%	59.8%	89.8%
Terminal rate	12/36 (33%)	10/27 (37%)	7/23 (30%)	3/5 (60%)
First incidence (days)	481	404	388	432
Life table test	P<0.001	P=0.256	P=0.033	P<0.001
Logistic regression test	P=0.128	P=0.549	P=0.421	P=0.104
Cochran-Armitage test	P=0.029			
Fisher exact test		P=0.534	P=0.238	P=0.057

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	51/51 (100%)	53/53 (100%)	52/52 (100%)
Adjusted rate	90.0%	100.0%	100.0%	100.0%
Terminal rate	31/36 (86%)	27/27 (100%)	23/23 (100%)	5/5 (100%)
First incidence (days)	460	404	388	369
Life table test	P<0.001	P=0.013	P<0.001	P<0.001
Logistic regression test	P=0.039	P=0.062	P=0.084	P=0.437
Cochran-Armitage test	P=0.008			
Fisher exact test		P=0.027	P=0.024	P=0.025

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, esophagus, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls			
	Fibroadenoma	Adenoma	Carcinoma	Fibroadenoma, Adenoma, or Carcinoma
Historical Incidence at Southern Research Institute				
Benzyl Acetate	12/50	0/50	0/50	12/50
C.I. Pigment Red 23	23/50	0/50	1/50	23/50
C.I. Pigment Red 3	23/50	0/50	4/50	26/50
Nitrofurantoin	28/50	0/50	6/50	30/50
o-Nitroanisole	17/50	1/50	2/50	18/50
p-Nitrobenzoic Acid	22/50	1/50	2/50	25/50
Polysorbate 80	28/50	1/50	0/50	29/50
Rhodamine 6G	19/50	1/50	3/50	23/50
Roxarsone	21/50	0/50	4/50	24/50
Overall Historical Incidence				
Total	521/1,351 (38.6%)	23/1,351 (1.7%)	41/1,351 (3.0%)	568/1,351 (42.0%)
Standard deviation	13.1%	2.3%	3.2%	14.0%
Range	8%-58%	0%-8%	0%-12%	8%-64%

[a] Data as of 31 March 1993

TABLE B4b
Historical Incidence of Zymbal's Gland Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	1/50	1/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	1/50	1/50
o-Nitroanisole	0/50	1/50	1/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	1/50	1/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/1,351 (0.1%)	8/1,351 (0.6%)	9/1,351 (0.7%)
Standard deviation	0.4%	1.1%	1.1%
Range	0%-2%	0%-4%	0%-4%

[a] Data as of 31 March 1993

TABLE B4c
Historical Incidence of Pharynx Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	3/1,351 (0.2%)	2/1,351 (0.2%)	5/1,351 (0.4%)
Standard deviation	0.6%	0.5%	0.8%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of 31 March 1993

TABLE B4d
Historical Incidence of Tongue Squamous Cell Papilloma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	1/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	1/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	0/50
Overall Historical Incidence	
Total	5/1,351 (0.4%)
Standard deviation	0.8%
Range	0%-2%

[a] Data as of 31 March 1993

TABLE B4e
Historical Incidence of Oral Cavity Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Papilloma or Squamous Cell Papilloma	Squamous Cell Carcinoma	Papilloma, Squamous Cell Papilloma, or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	1/50	0/50	1/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	1/50	0/50	1/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	8/1,351 (0.6%)	4/1,351 (0.3%)	12/1,351 (0.9%)
Standard deviation	1.1%	0.7%	1.4%
Range	0%-4%	0%-2%	0%-6%

[a] Data as of 31 March 1993 for oral mucosa, tongue, pharynx, tooth, and lip

TABLE B4f
Historical Incidence of Forestomach Squamous Cell Papilloma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	0/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	1/50
Overall Historical Incidence	
Total	2/1,351 (0.2%)
Standard deviation	0.5%
Range	0%-2%

[a] Data as of 31 March 1993

TABLE B4g
Historical Incidence of Small Intestine Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/1,351 (0.0%)	0/1,351 (0.0%)	0/1,351 (0.0%)

[a] Data as of 31 March 1993 for duodenum, ileum, and jejunum

TABLE B4h
Historical Incidence of Large Intestine Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/1,351 (0.0%)	0/1,351 (0.0%)	0/1,351 (0.0%)

[a] Data as of 31 March 1993 for cecum, colon, and rectum

TABLE B4i
Historical Incidence of Renal Tubule Adenoma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	0/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	0/50
Overall Historical Incidence	
Total	1/1,348 (0.1%)
Standard deviation	0.4%
Range	0%-2%

[a] Data as of 31 March 1993

TABLE B4j
Historical Incidence of Lung Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls			
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma	Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute				
Benzyl Acetate	0/50	1/50	1/50	0/50
C.I. Pigment Red 23	0/50	1/50	1/50	0/50
C.I. Pigment Red 3	1/50	0/50	1/50	0/50
Nitrofurantoin	2/50	1/50	3/50	0/50
o-Nitroanisole	0/50	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	1/50	1/50	0/50
Polysorbate 80	1/50	0/50	1/50	0/50
Rhodamine 6G	0/50	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50	0/50
Overall Historical Incidence				
Total	21/1,351 (1.6%)	5/1,351 (0.4%)	26/1,351 (1.9%)	0/1,350 (0.0%)
Standard deviation	2.2%	0.8%	2.3%	
Range	0%-10%	0%-2%	0%-10%	

[a] Data as of 31 March 1993

TABLE B4k
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	1/50	1/50
C.I. Pigment Red 23	0/50	1/50	1/50
C.I. Pigment Red 3	1/50	0/50	1/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	1/50	1/50	2/50
Rhodamine 6G	1/50	0/50	1/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	5/1,346 (0.4%)	7/1,346 (0.5%)	12/1,346 (0.9%)
Standard deviation	0.8%	1.1%	1.5%
Range	0%-2%	0%-4%	0%-6%

[a] Data as of 31 March 1993

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	7	8
Early deaths				
Moribund	14	22	27	41
Natural deaths		2	3	6
Survivors				
Terminal sacrifice	36	27	23	5
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(9)	(7)	(8)
Angiectasis				1 (13%)
Eosinophilic focus	1 (10%)			
Focal cellular change	3 (30%)	7 (78%)	5 (71%)	6 (75%)
Hepatodiaphragmatic nodule	1 (10%)	2 (22%)	1 (14%)	1 (13%)
Hepatodiaphragmatic nodule, multiple			1 (14%)	
Inflammation, focal	6 (60%)	1 (11%)	4 (57%)	5 (63%)
Bile duct, hyperplasia	2 (20%)			
Mesentery			(2)	
Fat, necrosis			2 (100%)	
Pancreas	(10)	(9)	(7)	(8)
Atrophy, focal	4 (40%)	4 (44%)	3 (43%)	2 (25%)
Endocrine System				
Adrenal cortex	(10)	(9)	(7)	(8)
Accessory adrenal cortical nodule	1 (10%)			
Focal cellular change			1 (14%)	
Pituitary gland	(9)	(9)	(7)	(8)
Angiectasis	6 (67%)	4 (44%)	2 (29%)	3 (38%)
Cyst	1 (11%)	2 (22%)	2 (29%)	
Pars distalis, angiectasis	1 (11%)			
Pars distalis, cyst		1 (11%)		
Pars distalis, focal cellular change	1 (11%)	2 (22%)	1 (14%)	2 (25%)
Pars distalis, hyperplasia			1 (14%)	
Pars distalis, hyperplasia, focal	2 (22%)		1 (14%)	2 (25%)
Thyroid gland	(10)	(9)	(7)	(8)
Ultimobranchial cyst			1 (14%)	
Genital System				
Clitoral gland	(10)	(9)	(7)	(8)
Degeneration, cystic	8 (80%)	5 (56%)	5 (71%)	6 (75%)
Hyperplasia	2 (20%)			
Inflammation, chronic				1 (13%)
Ovary	(10)	(9)	(7)	(8)
Cyst	1 (10%)	1 (11%)		1 (13%)
Bilateral, cyst		1 (11%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
15-Month Interim Evaluation (continued)				
Genital System (continued)				
Uterus	(10)	(9)	(7)	(8)
Hydrometra	1 (10%)	2 (22%)		
Endometrium, hyperplasia, cystic	1 (10%)	1 (11%)		2 (25%)
Integumentary System				
Mammary gland	(10)	(9)	(7)	(8)
Dilatation	2 (20%)	4 (44%)	2 (29%)	4 (50%)
Hyperplasia				1 (13%)
Musculoskeletal System				
Bone	(10)	(9)	(7)	(8)
Hyperostosis	2 (20%)	2 (22%)	1 (14%)	
Respiratory System				
Lung	(10)	(9)	(7)	(8)
Alveolar epithelium, hyperplasia			1 (14%)	
Nose	(10)	(9)	(7)	(8)
Inflammation, suppurative	1 (10%)			
Nasolacrimal duct, cyst				1 (13%)
Urinary System				
Kidney	(10)	(9)	(7)	(8)
Nephropathy	8 (80%)	7 (78%)	6 (86%)	7 (88%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Hematopoietic System				
Nervous System				
Special Senses System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(51)	(53)	(52)
Epithelium, hyperplasia, focal				1 (2%)
Intestine large, colon	(50)	(51)	(53)	(52)
Intussusception		1 (2%)		
Parasite metazoan	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Intestine large, rectum	(49)	(51)	(53)	(52)
Parasite metazoan	2 (4%)	4 (8%)		2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(51)	(53)	(52)
Angiectasis	2 (4%)		1 (2%)	1 (2%)
Autolysis				1 (2%)
Basophilic focus	1 (2%)			
Congestion, focal			1 (2%)	
Developmental malformation		1 (2%)		
Fatty change	9 (18%)	12 (24%)	11 (21%)	8 (15%)
Focal cellular change	39 (78%)	41 (80%)	38 (72%)	36 (69%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		3 (6%)
Hemorrhage, focal			1 (2%)	
Hepatodiaphragmatic nodule	5 (10%)	3 (6%)	2 (4%)	8 (15%)
Hepatodiaphragmatic nodule, multiple				1 (2%)
Hyperplasia, histiocytic			1 (2%)	
Hyperplasia, histiocytic, lymphoid			1 (2%)	
Infiltration cellular, mixed cell	4 (8%)	1 (2%)	6 (11%)	6 (12%)
Inflammation, focal	14 (28%)	18 (35%)	15 (28%)	14 (27%)
Necrosis, focal	1 (2%)		2 (4%)	7 (13%)
Bile duct, hyperplasia	24 (48%)	24 (47%)	21 (40%)	19 (37%)
Biliary tract, cyst		1 (2%)		
Centrilobular, atrophy	11 (22%)	10 (20%)	10 (19%)	15 (29%)
Centrilobular, congestion			1 (2%)	
Centrilobular, degeneration				1 (2%)
Hepatocyte, hyperplasia, multifocal	8 (16%)	10 (20%)	7 (13%)	7 (13%)
Mesentery	(6)	(12)	(7)	(6)
Accessory spleen	1 (17%)			
Inflammation, chronic				2 (33%)
Fat, necrosis	2 (33%)	9 (75%)	5 (71%)	3 (50%)
Pancreas	(50)	(51)	(53)	(52)
Accessory spleen	1 (2%)	1 (2%)	1 (2%)	
Atrophy, focal	20 (40%)	13 (25%)	19 (36%)	14 (27%)
Fibrosis, focal	1 (2%)			
Duct, dilatation		1 (2%)		
Pharynx	(1)	(1)	(1)	(2)
Palate, epithelium, hyperplasia, focal				1 (50%)
Stomach, forestomach	(50)	(51)	(53)	(52)
Edema	1 (2%)	1 (2%)		
Erosion				1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)		1 (2%)
Pigmentation				1 (2%)
Ulcer		1 (2%)		1 (2%)
Ulcer, multiple	1 (2%)			
Mucosa, hyperplasia	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(51)	(53)	(52)
Edema	1 (2%)	1 (2%)		
Erosion	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pigmentation, focal		1 (2%)		
Tongue	(1)	(3)	(6)	(6)
Inflammation, chronic, focal				1 (17%)
Epithelium, hyperplasia, focal		1 (33%)	1 (17%)	1 (17%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Tooth			(2)	
Developmental malformation			1 (50%)	
Incisor, dysplasia			1 (50%)	
Cardiovascular System				
Heart	(49)	(51)	(53)	(52)
Thrombosis			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(51)	(53)	(52)
Accessory adrenal cortical nodule	4 (8%)	4 (8%)	4 (8%)	3 (6%)
Angiectasis	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Congestion			3 (6%)	2 (4%)
Focal cellular change	11 (22%)	16 (31%)	7 (13%)	11 (21%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, histiocytic	2 (4%)			
Hyperplasia, lymphoid	2 (4%)			
Vacuolization cytoplasmic	1 (2%)		1 (2%)	
Adrenal medulla	(50)	(51)	(53)	(52)
Hyperplasia	2 (4%)	1 (2%)	4 (8%)	2 (4%)
Parathyroid gland	(47)	(50)	(53)	(52)
Cyst		1 (2%)		
Hyperplasia			2 (4%)	
Pituitary gland	(49)	(51)	(52)	(51)
Angiectasis	12 (24%)	6 (12%)	7 (13%)	6 (12%)
Cyst	6 (12%)	10 (20%)	10 (19%)	12 (24%)
Hemorrhage			1 (2%)	
Pars distalis, angiectasis		1 (2%)		1 (2%)
Pars distalis, focal cellular change	7 (14%)	3 (6%)	6 (12%)	
Pars distalis, hyperplasia, focal	7 (14%)	4 (8%)		4 (8%)
Pars distalis, pigmentation		1 (2%)		
Thyroid gland	(50)	(51)	(53)	(52)
Ultimobranchial cyst	1 (2%)			4 (8%)
C-cell, hyperplasia	8 (16%)	14 (27%)	18 (34%)	14 (27%)
Follicle, dilatation				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(48)	(49)	(49)	(52)
Degeneration, cystic	40 (83%)	45 (92%)	41 (84%)	50 (96%)
Dilatation			1 (2%)	
Hyperplasia	2 (4%)	4 (8%)	4 (8%)	1 (2%)
Inflammation, chronic	2 (4%)	2 (4%)	2 (4%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Ovary	(50)	(51)	(53)	(52)
Angiectasis		1 (2%)		
Cyst	6 (12%)	3 (6%)	5 (9%)	6 (12%)
Corpus luteum, hyperplasia, lymphoid	2 (4%)		3 (6%)	1 (2%)
Corpus luteum, thecal cell, hyperplasia	2 (4%)		3 (6%)	1 (2%)
Uterus	(50)	(51)	(53)	(52)
Hydrometra	1 (2%)			4 (8%)
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Cervix, hyperplasia				1 (2%)
Endometrium, cyst	1 (2%)	2 (4%)	4 (8%)	2 (4%)
Endometrium, hyperplasia, cystic	3 (6%)	1 (2%)	2 (4%)	5 (10%)
Endometrium, inflammation	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(51)	(53)	(52)
Hypercellularity	5 (10%)	4 (8%)	11 (21%)	10 (19%)
Hyperplasia, focal, histiocytic				1 (2%)
Metaplasia, osseous		1 (2%)		
Myelofibrosis	1 (2%)	1 (2%)		
Lymph node	(16)	(11)	(15)	(19)
Axillary, hyperplasia				1 (5%)
Deep cervical, hyperplasia			1 (7%)	
Iliac, inflammation, suppurative				1 (5%)
Inguinal, hyperplasia	1 (6%)			1 (5%)
Mediastinal, hemorrhage	6 (38%)	3 (27%)	1 (7%)	2 (11%)
Mediastinal, hyperplasia			1 (7%)	
Mediastinal, pigmentation		1 (9%)		1 (5%)
Pancreatic, hemorrhage			1 (7%)	
Renal, hyperplasia				1 (5%)
Renal, pigmentation				1 (5%)
Lymph node, mandibular	(49)	(48)	(53)	(50)
Hemorrhage		1 (2%)		1 (2%)
Hyperplasia		1 (2%)	1 (2%)	
Lymph node, mesenteric	(50)	(51)	(53)	(52)
Hemorrhage	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia			1 (2%)	
Spleen	(50)	(51)	(53)	(52)
Angiectasis	1 (2%)			
Congestion		2 (4%)		
Fibrosis, focal	1 (2%)		4 (8%)	5 (10%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	7 (13%)	10 (19%)
Necrosis, focal	1 (2%)			
Thymus	(49)	(50)	(51)	(52)
Congestion			1 (2%)	
Cyst	2 (4%)	2 (4%)		
Hemorrhage			2 (4%)	
Hyperplasia, lymphoid		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(51)	(53)	(52)
Dilatation	42 (84%)	41 (80%)	35 (66%)	30 (58%)
Hyperplasia	7 (14%)	12 (24%)	8 (15%)	9 (17%)
Inflammation, chronic		1 (2%)		
Skin	(50)	(51)	(53)	(52)
Alopecia		1 (2%)		
Hyperkeratosis, focal	1 (2%)			
Epidermis, hyperplasia, focal	1 (2%)			
Subcutaneous tissue, inflammation, chronic, focal		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(51)	(53)	(52)
Hyperostosis	8 (16%)	8 (16%)	9 (17%)	4 (8%)
Nervous System				
Brain	(49)	(51)	(53)	(52)
Compression	9 (18%)	10 (20%)	9 (17%)	4 (8%)
Hemorrhage	1 (2%)		2 (4%)	1 (2%)
Respiratory System				
Lung	(50)	(51)	(53)	(52)
Congestion		1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal	1 (2%)			
Hemorrhage, diffuse				1 (2%)
Hyperplasia, focal, macrophage	1 (2%)			
Inflammation, chronic, focal		1 (2%)	2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)		3 (6%)	4 (8%)
Pleura, inflammation, chronic, focal		1 (2%)		
Nose	(49)	(51)	(53)	(52)
Fungus		1 (2%)	3 (6%)	1 (2%)
Inflammation, suppurative		2 (4%)	4 (8%)	2 (4%)
Mucosa, hyperplasia, focal				1 (2%)
Nasolacrimal duct, cyst			1 (2%)	
Nasolacrimal duct, inflammation, chronic active			1 (2%)	
Special Senses System				
Eye	(3)	(1)	(3)	
Atrophy	2 (67%)		1 (33%)	
Cataract	3 (100%)	1 (100%)	1 (33%)	
Fibrosis	1 (33%)			
Hemorrhage			1 (33%)	
Inflammation, chronic			1 (33%)	
Necrosis, focal			1 (33%)	
Synechia	1 (33%)			
Retina, degeneration	2 (67%)	1 (100%)	1 (33%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(51)	(53)	(52)
Atrophy, focal		2 (4%)	1 (2%)	7 (13%)
Cyst	1 (2%)			1 (2%)
Inflammation, chronic, suppurative	1 (2%)			
Nephropathy	48 (96%)	50 (98%)	50 (94%)	50 (96%)
Papilla, degeneration		1 (2%)	3 (6%)	17 (33%)
Papilla, epithelium, hyperplasia		1 (2%)	1 (2%)	7 (13%)
Pelvis, dilatation				1 (2%)
Pelvis, transitional epithelium, hyperplasia		1 (2%)		
Renal tubule, epithelium, hyperplasia, focal		1 (2%)		
Urinary bladder	(50)	(51)	(53)	(52)
Dilatation				1 (2%)
Inflammation, chronic				1 (2%)
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	10
Early deaths				
Accidental death				1
Moribund	3	12	11	13
Natural deaths	5	3	4	5
Survivors				
Terminal sacrifice	42	36	35	30
Missing				1
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Intestine small, ileum	(10)	(9)	(10)	(10)
Carcinoma		1 (11%)		
Liver	(10)	(9)	(10)	(10)
Hepatocellular carcinoma				2 (20%)
Hepatocellular adenoma	4 (40%)	4 (44%)	1 (10%)	2 (20%)
Stomach, forestomach	(10)	(9)	(10)	(10)
Squamous cell papilloma				1 (10%)
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Alveolar/bronchiolar adenoma	2 (20%)	1 (11%)	4 (40%)	
Alveolar/bronchiolar carcinoma				1 (10%)
Special Senses System				
Harderian gland	(4)	(6)	(5)	(4)
Adenoma			1 (20%)	2 (50%)
Bilateral, adenoma				1 (25%)
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study				
Alimentary System				
Gallbladder	(48)	(44)	(49)	(44)
Fibrous histiocytoma		1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)		
Intestine large, cecum	(49)	(49)	(48)	(48)
Intestine small, duodenum	(49)	(50)	(49)	(46)
Intestine small, jejunum	(49)	(49)	(49)	(48)
Carcinoma				2 (4%)
Intestine small, ileum	(48)	(48)	(47)	(48)
Liver	(49)	(51)	(49)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma	1 (2%)			
Hemangioma		1 (2%)		1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)		2 (4%)
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	11 (22%)	15 (29%)	14 (29%)	7 (14%)
Hepatocellular carcinoma, multiple		2 (4%)	1 (2%)	
Hepatocellular adenoma	12 (24%)	15 (29%)	11 (22%)	10 (20%)
Hepatocellular adenoma, multiple	6 (12%)	5 (10%)	8 (16%)	9 (18%)
Histiocytic sarcoma		2 (4%)		
Squamous cell carcinoma, metastatic, stomach, forestomach				2 (4%)
Mesentery	(3)	(2)	(1)	(3)
Hemangiosarcoma				1 (33%)
Hepatoblastoma, metastatic, liver		1 (50%)		
Histiocytic sarcoma		1 (50%)		
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (33%)
Pancreas	(49)	(51)	(49)	(49)
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)
Pharynx			(1)	
Squamous cell papilloma			1 (100%)	
Stomach, forestomach	(49)	(51)	(50)	(48)
Squamous cell carcinoma			1 (2%)	2 (4%)
Squamous cell papilloma		3 (6%)	2 (4%)	2 (4%)
Stomach, glandular	(49)	(51)	(49)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cardiovascular System				
Heart	(50)	(51)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(48)	(51)	(50)	(49)
Adenoma		1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Histiocytic sarcoma		1 (2%)		
Capsule, adenoma	1 (2%)			
Adrenal medulla	(49)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(49)	(50)	(49)	(49)
Adenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Pituitary gland	(48)	(46)	(50)	(46)
Pars distalis, carcinoma				1 (2%)
Thyroid gland	(49)	(51)	(49)	(49)
Follicular cell, adenoma		3 (6%)		4 (8%)
Follicular cell, carcinoma	1 (2%)			
General Body System				
None				
Genital System				
Epididymis	(49)	(51)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Preputial gland	(48)	(49)	(49)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Seminal vesicle	(49)	(51)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Testes	(49)	(51)	(50)	(49)
Hemangioma				1 (2%)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(51)	(50)	(49)
Hemangiosarcoma		2 (4%)		
Histiocytic sarcoma		1 (2%)		
Lymph node	(3)	(3)	(5)	(6)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (20%)	
Lymph node, mandibular	(46)	(49)	(49)	(46)
Lymph node, mesenteric	(48)	(49)	(49)	(48)
Histiocytic sarcoma		2 (4%)		
Spleen	(49)	(51)	(49)	(49)
Hemangiosarcoma		3 (6%)		
Histiocytic sarcoma		1 (2%)		
Thymus	(44)	(48)	(40)	(42)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(51)	(50)	(49)
Mast cell tumor benign				1 (2%)
Squamous cell papilloma		1 (2%)		
Sebaceous gland, adenoma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma			2 (4%)	
Musculoskeletal System				
Skeletal muscle		(1)		(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)
Hepatocellular carcinoma, metastatic, liver		1 (100%)		
Nervous System				
Brain	(50)	(51)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Respiratory System				
Lung	(50)	(51)	(50)	(49)
Alveolar/bronchiolar adenoma	12 (24%)	4 (8%)	8 (16%)	11 (22%)
Alveolar/bronchiolar adenoma, multiple			4 (8%)	10 (20%)
Alveolar/bronchiolar carcinoma	3 (6%)	6 (12%)	8 (16%)	8 (16%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		3 (6%)
Carcinoma, metastatic, harderian gland	1 (2%)			1 (2%)
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	5 (10%)	3 (6%)	3 (6%)
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)
Nose	(49)	(51)	(50)	(49)
Special Senses System				
Harderian gland	(22)	(25)	(28)	(32)
Adenoma	3 (14%)	6 (24%)	11 (39%)	10 (31%)
Carcinoma	1 (5%)	1 (4%)	4 (14%)	3 (9%)
Bilateral, adenoma			1 (4%)	8 (25%)
Bilateral, carcinoma				1 (3%)
Zymbal's gland				(1)
Carcinoma				1 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(49)	(51)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma, metastatic, stomach, forestomach				1 (2%)
Renal tubule, adenoma			3 (6%)	2 (4%)
Urinary bladder	(49)	(51)	(49)	(49)
Hemangiosarcoma	1 (2%)			1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(51)	(50)	(49)
Histiocytic sarcoma		2 (4%)		
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	2 (4%)	2 (4%)	6 (12%)	3 (6%)
Lymphoma malignant undifferentiated cell		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	6	5	6	8
2-Year study	37	42	45	45
Total primary neoplasms				
15-Month interim evaluation	6	6	6	9
2-Year study	57	84	86	107
Total animals with benign neoplasms				
15-Month interim evaluation	6	4	6	6
2-Year study	30	29	38	43
Total benign neoplasms				
15-Month interim evaluation	6	5	6	6
2-Year study	36	42	50	71
Total animals with malignant neoplasms				
15-Month interim evaluation		1		3
2-Year study	17	31	24	30
Total malignant neoplasms				
15-Month interim evaluation		1		3
2-Year study	21	42	36	36
Total animals with metastatic neoplasms				
2-Year study	3	6	4	7
Total metastatic neoplasms				
2-Year study	5	11	4	19

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm

Number of Days on Study	3 1 0	4 7 8	5 7 9	6 0 6	6 1 4	6 3 9	6 7 4	7 0 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 0 3	0 2 5	0 3 6	0 0 4	0 3 4	0 2 8	0 4 0	0 1 8	0 1 1	0 0 2	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 9	0 2 0
Alimentary System																										
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																										
Hemangiosarcoma																										
Hepatocellular carcinoma		X	X	X	X	X	X		X		X											X				
Hepatocellular adenoma										X		X		X										X	X	X
Hepatocellular adenoma, multiple				X				X												X						
Mesentery																						+				
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+						+	+						+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland							X																			
Endocrine System																										
Adrenal cortex	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																										
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																		X								
General Body System																										
Tissue NOS																										
Genital System																										
Coagulating gland								+																		
Epididymis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Prostate	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									X	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	
Carcass ID Number	0 2 1	0 2 2	0 2 3	0 2 4	0 2 6	0 2 7	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 5	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cholangiocarcinoma							X																			1
Hemangiosarcoma						X																				1
Hepatocellular carcinoma							X								X											11
Hepatocellular adenoma		X					X			X										X		X		X		12
Hepatocellular adenoma, multiple				X		X		X																		6
Mesentery																							+		+	3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+			+		+			+						+				+	+		+	+	13
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Capsule, adenoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X															1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS				+																						1
Genital System																										
Coagulating gland						+																				2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	3 1 0	4 7 8	5 7 9	6 0 6	6 1 4	6 3 9	6 7 4	7 0 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 0 3	0 2 5	0 3 6	0 0 4	0 3 4	0 2 8	0 4 0	0 1 8	0 0 1	0 0 2	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 9	0 2 0
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																		+	+						
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X						X									X	X			X	X			
Alveolar/bronchiolar carcinoma																				X			X		
Carcinoma, metastatic, harderian gland							X																		
Hepatocellular carcinoma, metastatic, liver			X		X																				
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland		+				+	+			+	+		+			+	+	+					+	+	
Adenoma																									
Carcinoma							X																		
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland							X																		
Urethra								+																	
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 2 1	0 2 2	0 2 3	0 2 4	0 2 6	0 2 7	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 5	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node											+															3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X		X	X						X			X				12
Alveolar/bronchiolar carcinoma						X																				3
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland			+			+	+	+	+	+	+	+	+	+							+					22
Adenoma													X	X							X					3
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed													X											X		2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm

Number of Days on Study	0	0	3	4	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	1	1	6	6	4	8	9	2	2	4	5	7	8	0	3	3	3	3	3	3	3	3	3	3	3
	7	9	2	1	3	6	2	5	5	6	6	8	3	5	1	7	7	7	7	7	7	7	7	7	7
Carcass ID Number	0	0	1	0	0	1	0	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	8	7	1	9	9	0	7	7	0	0	8	0	9	0	7	6	6	6	6	6	6	6	6	6	7
	2	0	6	8	9	7	4	6	5	1	6	0	3	4	7	1	2	3	4	5	6	7	8	9	1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	M	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Fibrous histiocytoma												X													
Hepatoblastoma, metastatic, liver												X													
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Hemangiosarcoma																		X							
Hepatoblastoma												X													
Hepatocellular carcinoma					X		X	X	X				X							X				X	
Hepatocellular carcinoma, multiple												X													
Hepatocellular adenoma				X			X							X									X	X		X
Hepatocellular adenoma, multiple																	X	X							
Histiocytic sarcoma						X									X										
Mesentery						+						+													
Hepatoblastoma, metastatic, liver												X													
Histiocytic sarcoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																	+								
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Histiocytic sarcoma															X										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																	X								
Islets, pancreatic	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+
Pituitary gland	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 7 2	0 7 3	0 7 5	0 7 8	0 7 9	0 8 0	0 8 1	0 8 3	0 8 4	0 8 5	0 8 7	0 8 8	0 8 9	0 9 0	0 9 1	0 9 2	0 9 4	0 9 5	0 9 6	0 9 7	1 0 2	1 0 3	1 0 6	1 0 8	1 0 9	1 1 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Fibrous histiocytoma																											1
Hepatoblastoma, metastatic, liver																											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangioma																											1
Hemangiosarcoma								X																			2
Hepatoblastoma																											1
Hepatocellular carcinoma		X			X	X		X		X										X			X			X	15
Hepatocellular carcinoma, multiple																		X									2
Hepatocellular adenoma		X		X					X	X	X	X				X					X	X					15
Hepatocellular adenoma, multiple					X												X									X	5
Histiocytic sarcoma																											2
Mesentery																											2
Hepatoblastoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma					X																				X		3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth									+																		2
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											1
Histiocytic sarcoma																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant												X															1
Pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X																1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma					X	X																					3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	0	0	3	4	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	1	1	6	6	4	8	9	2	2	4	5	7	8	0	3	3	3	3	3	3	3	3	3	3
	7	9	2	1	3	6	2	5	5	6	6	8	3	5	1	7	7	7	7	7	7	7	7	7
Carcass ID Number	0	0	1	0	0	1	0	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
	8	7	1	9	9	0	7	7	0	0	8	0	9	0	7	6	6	6	6	6	6	6	6	7
	2	0	6	8	9	7	4	6	5	1	6	0	3	4	7	1	2	3	4	5	6	7	8	9	1
General Body System																								
None																								
Genital System																								
Coagulating gland																					+			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																		
Preputial gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma															X									
Lymph node			+																					
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Histiocytic sarcoma						X									X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma															X									
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X			
Sebaceous gland, adenoma																								X
Subcutaneous tissue, hemangiosarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+															
Hepatocellular carcinoma, metastatic, liver									X															
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver									X															
Spinal cord																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 7 2	0 7 3	0 7 5	0 7 8	0 7 9	0 8 0	0 8 1	0 8 3	0 8 4	0 8 5	0 8 7	0 8 8	0 8 9	0 9 0	0 9 1	0 9 2	0 9 4	0 9 5	0 9 6	0 9 7	1 0 2	1 0 3	1 0 6	1 0 8	1 0 9	1 1 0	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Coagulating gland																									+		2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma			X					X																			2
Histiocytic sarcoma																											1
Lymph node				+																					+		3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma			X					X														X					3
Histiocytic sarcoma																											1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																											1
Sebaceous gland, adenoma																											1
Subcutaneous tissue, hemangiosarcoma																						X					1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma, metastatic, liver																											1
Spinal cord										+																	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	0	0	3	4	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	1	1	6	6	4	8	9	2	2	4	5	7	8	0	3	3	3	3	3	3	3	3	3	3
	7	9	2	1	3	6	2	5	5	6	6	8	3	5	1	7	7	7	7	7	7	7	7	7
Carcass ID Number	0	0	1	0	0	1	0	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
	8	7	1	9	9	0	7	7	0	0	8	0	9	0	7	6	6	6	6	6	6	6	6	7
	2	0	6	8	9	7	4	6	5	1	6	0	3	4	7	1	2	3	4	5	6	7	8	9	1
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X														X				
Alveolar/bronchiolar carcinoma										X												X		
Alveolar/bronchiolar carcinoma, multiple																								
Hepatoblastoma, metastatic, liver												X												
Hepatocellular carcinoma, metastatic, liver								X	X				X							X				
Histiocytic sarcoma															X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye											+													
Harderian gland			+			+	+	+		+	+		+	+		+	+	+		+	+		+	+	
Adenoma											X			X		X					X			
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X													
Histiocytic sarcoma															X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X									X									
Lymphoma malignant mixed																								
Lymphoma malignant undifferentiated cell type																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 7 2	0 7 3	0 7 5	0 7 8	0 7 9	0 8 0	0 8 1	0 8 3	0 8 4	0 8 5	0 8 7	0 8 8	0 8 9	0 9 0	0 9 1	0 9 2	0 9 4	0 9 5	0 9 6	0 9 7	1 0 2	1 0 3	1 0 6	1 0 8	1 0 9	1 1 0	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma					X																	X					4
Alveolar/bronchiolar carcinoma				X								X		X			X										6
Alveolar/bronchiolar carcinoma, multiple	X																										1
Hepatoblastoma, metastatic, liver																											1
Hepatocellular carcinoma, metastatic, liver						X																					5
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye																				+							2
Harderian gland	+	+	+			+						+					+	+	+	+	+						25
Adenoma						X														X							6
Carcinoma			X																								1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																											1
Histiocytic sarcoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																											2
Lymphoma malignant mixed					X			X																			2
Lymphoma malignant undifferentiated cell type																									X		1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm

Number of Days on Study	0 4 5	5 3 6	5 7 2	5 7 9	6 2 6	6 6 2	6 6 6	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 7 7	6 8 7	7 3 1	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	1 6 0	1 6 5	1 5 5	1 2 5	1 3 8	1 5 2	1 6 9	1 6 7	1 4 8	1 5 8	1 6 4	1 7 1	1 2 4	1 4 9	1 4 5	1 2 1	1 2 2	1 2 3	1 2 6	1 2 7	1 2 8	1 2 9	1 3 0	1 3 1	1 3 2
Alimentary System																								
Esophagus	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X		X		X		X			X	X	X					X	X	X			
Hepatocellular carcinoma, multiple							X																	
Hepatocellular adenoma										X				X		X				X	X	X		
Hepatocellular adenoma, multiple		X						X									X	X						
Mesentery																	+							
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx					+																			
Squamous cell papilloma					X																			
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X				
Squamous cell papilloma																								
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 9	1 4 0	1 4 1	1 4 2	1 4 3	1 4 4	1 4 6	1 4 7	1 5 0	1 5 1	1 5 3	1 5 4	1 5 6	1 5 7	1 5 9	1 6 1	1 6 2	1 6 3	1 6 6	1 6 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma			X												X			X				X				14
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X			X		X				X			X													11
Hepatocellular adenoma, multiple							X		X		X							X								8
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Squamous cell papilloma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma	X								X																	2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth						+			+						+									+		4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	0 4 5	5 3 6	5 7 2	5 7 9	6 2 6	6 6 2	6 6 6	6 6 8	6 6 9	6 6 9	6 6 9	6 6 7	6 7 7	6 8 1	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	1 6 0	1 6 5	1 5 5	1 2 5	1 3 8	1 5 2	1 6 9	1 6 7	1 4 8	1 5 8	1 6 4	1 7 1	1 2 4	1 4 9	1 4 5	1 2 1	1 2 2	1 2 3	1 2 6	1 2 7	1 2 8	1 2 9	1 3 0	1 3 1	1 3 2
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+			+								+											
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Lymph node, mandibular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal			+			+																			
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	I	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X										X					X				X			
Alveolar/bronchiolar adenoma, multiple		X																							
Alveolar/bronchiolar carcinoma			X				X		X								X					X			
Hepatocellular carcinoma, metastatic, liver													X		X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+														
Harderian gland			+	+	+		+		+	+	+	+	+			+			+	+			+	+	+
Adenoma									X		X	X											X		X
Carcinoma							X			X								X				X			
Bilateral, adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma										X									X						
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X		X						X		X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 9	1 4 0	1 4 1	1 4 2	1 4 3	1 4 4	1 4 6	1 4 7	1 5 0	1 5 1	1 5 3	1 5 4	1 5 6	1 5 7	1 5 9	1 6 1	1 6 2	1 6 3	1 6 6	1 6 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node									+																+	5
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal																									+	3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+	M	40
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma			X																						X	2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X										X					X	X								8
Alveolar/bronchiolar adenoma, multiple						X													X						X	4
Alveolar/bronchiolar carcinoma		X																X		X						8
Hepatocellular carcinoma, metastatic, liver			X																							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye														+		+							+			4
Harderian gland	+		+		+		+			+		+		+	+	+			+			+			+	28
Adenoma			X		X					X				X		X									X	11
Carcinoma																										4
Bilateral, adenoma							X																			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma		X																								3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed					X																				X	6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm

Number of Days on Study	2 4 8	4 4 5	4 4 7	5 1 5	5 6 5	5 8 9	5 9 2	5 9 2	5 9 3	6 4 1	6 5 6	6 6 9	6 6 9	6 6 9	6 6 3	7 0 5	7 0 5	7 2 5	7 2 5	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8
Carcass ID Number	2 0 5	1 9 0	2 0 6	2 0 2	1 9 2	1 8 4	1 8 7	2 1 5	1 9 7	1 2 6	2 2 2	1 8 1	1 8 9	1 9 6	2 1 3	1 8 5	2 2 1	1 9 4	1 9 8	1 8 2	1 8 3	1 8 6	1 8 8	1 9 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	I	+	+	+	M	M	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma														X										
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X														
Hemangioma																								
Hemangiosarcoma																						X		
Hepatocellular carcinoma				X					X								X	X					X	
Hepatocellular adenoma			X		X											X			X		X		X	
Hepatocellular adenoma, multiple						X		X	X															
Squamous cell carcinoma, metastatic, stomach, forestomach														X									X	
Mesentery														+									+	
Hemangiosarcoma																								
Squamous cell carcinoma, metastatic, stomach, forestomach																							X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach														X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma														X									X	
Squamous cell papilloma																								
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X														
Tooth												+												
Cardiovascular System																								
Blood vessel				+																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X														
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X			X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 9 3	1 9 5	1 9 9	2 0 0	2 0 1	2 0 3	2 0 4	2 0 7	2 0 8	2 0 9	2 1 1	2 1 2	2 1 4	2 1 6	2 1 7	2 1 8	2 1 9	2 2 0	2 2 3	2 2 4	2 2 5	2 2 7	2 2 8	2 2 9	2 3 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																				X						2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangioma												X														1
Hemangiosarcoma																						X				2
Hepatocellular carcinoma							X																	X		7
Hepatocellular adenoma					X			X									X				X					10
Hepatocellular adenoma, multiple									X			X		X				X		X				X		9
Squamous cell carcinoma, metastatic, stomach, forestomach																										2
Mesentery												+														3
Hemangiosarcoma												X														1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										2
Squamous cell papilloma					X												X									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Tooth									+				+													3
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	2 4 4 5 5 5 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 4 4 4 1 6 8 9 9 9 4 5 6 6 6 6 0 0 2 2 3 3 3 3 3 8 5 7 5 5 9 2 2 3 1 6 9 9 9 3 5 5 5 8 8 8 8 8
Carcass ID Number	2 1 2 2 1 1 1 2 1 2 2 1 1 1 2 1 2 1 1 1 1 1 1 1 0 9 0 0 9 8 8 1 9 2 2 8 8 9 1 8 2 9 9 8 8 8 8 9 5 0 6 2 2 4 7 5 7 6 2 1 9 6 3 5 1 4 8 2 3 6 8 1
Endocrine System (continued)	
Parathyroid gland	+ + + + + + + + + + + + + + M + + + + + + + + + +
Pituitary gland	M + + + + + + + M + + + + + + + M + + + + + + + +
Pars distalis, carcinoma	X
Thyroid gland	+ +
Follicular cell, adenoma	X X
General Body System	
None	
Genital System	
Epididymis	+ +
Preputial gland	+ +
Alveolar/bronchiolar carcinoma, metastatic, lung	X
Prostate	+ + + + + + + + + + + + + + M + + + + + + + + +
Seminal vesicle	+ +
Alveolar/bronchiolar carcinoma, metastatic, lung	X
Testes	+ +
Hemangioma	
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	M +
Lymph node, mediastinal	+
Spleen	+ +
Thymus	+ + + + + + M + + + + + + + + I + + + + + M + +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Mast cell tumor benign	
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Alveolar/bronchiolar carcinoma, metastatic, lung	X
Nervous System	
Brain	+ +
Alveolar/bronchiolar carcinoma, metastatic, lung	X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 9 3	1 9 5	1 9 9	2 0 0	2 0 1	2 0 3	2 0 4	2 0 7	2 0 8	2 0 9	2 1 1	2 1 2	2 1 4	2 1 6	2 1 7	2 1 8	2 1 9	2 2 0	2 2 3	2 2 4	2 2 5	2 2 7	2 2 8	2 2 9	2 3 0	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																				X		X				4
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma							X																			1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node											+						+									6
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal																	+									2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor benign																									X	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	24 48	44 45	44 47	51 55	55 59	58 59	59 62	59 72	59 93	64 01	65 26	66 29	66 98	66 99	66 99	70 03	70 25	72 55	72 55	73 88	73 88	73 88	73 88	73 88
Carcass ID Number	20 95	19 00	20 06	20 02	19 92	18 94	18 77	12 15	19 57	22 66	22 02	18 81	18 99	19 96	21 63	18 35	22 01	19 14	19 98	18 22	18 83	18 86	18 88	19 91
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X			X						X
Alveolar/bronchiolar adenoma, multiple									X		X	X		X										
Alveolar/bronchiolar carcinoma																							X	X
Alveolar/bronchiolar carcinoma, multiple										X					X									
Carcinoma, metastatic, harderian gland																		X						
Hepatocellular carcinoma, metastatic, liver									X								X							
Squamous cell carcinoma, metastatic, stomach, forestomach																							X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye											+		+		+				+	+				
Harderian gland	+				+	+				+	+	+	+	+	+	+	+	+	+	+		+	+	
Adenoma												X		X	X					X		X		
Carcinoma						X							X											
Bilateral, adenoma					X					X	X								X					
Bilateral, carcinoma																				X				
Zymbal's gland																								
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung										X														
Squamous cell carcinoma, metastatic, stomach, forestomach																							X	
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X		
Lymphoma malignant mixed								X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	
Carcass ID Number	1 9 3	1 9 5	1 9 9	2 0 0	2 0 1	2 0 3	2 0 4	2 0 7	2 0 8	2 0 9	2 1 1	2 1 2	2 1 4	2 1 6	2 1 7	2 1 8	2 1 9	2 2 0	2 2 3	2 2 4	2 2 5	2 2 7	2 2 8	2 2 9	2 3 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X	X	X					X				X	X				X						X			11
Alveolar/bronchiolar adenoma, multiple										X	X			X	X	X				X						10
Alveolar/bronchiolar carcinoma		X										X		X		X		X					X			8
Alveolar/bronchiolar carcinoma, multiple																									X	3
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																								X		3
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye					+			+											+		+					9
Harderian gland			+	+	+		+	+	+	+	+		+		+			+	+		+		+	+	+	32
Adenoma				X							X							X	X		X					10
Carcinoma					X																					3
Bilateral, adenoma							X	X		X														X		8
Bilateral, carcinoma																										1
Zymbal's gland																						+				1
Carcinoma																						X				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Renal tubule, adenoma										X													X			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																						1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed															X		X									3

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	6/51 (12%)	12/50 (24%)	18/49 (37%)
Adjusted rate[b]	7.1%	15.6%	31.0%	47.5%
Terminal rate[c]	3/42 (7%)	4/36 (11%)	9/35 (26%)	11/30 (37%)
First incidence (days)	736 (T)	656	669	565
Life table test[d]	P<0.001	P=0.182	P=0.006	P<0.001
Logistic regression test[d]	P<0.001	P=0.213	P=0.010	P<0.001
Cochran-Armitage test[d]	P<0.001			
Fisher exact test[d]		P=0.254	P=0.011	P<0.001
Harderian Gland: Carcinoma				
Overall rate	1/50 (2%)	1/51 (2%)	4/50 (8%)	4/49 (8%)
Adjusted rate	2.3%	2.8%	10.1%	10.9%
Terminal rate	0/42 (0%)	1/36 (3%)	2/35 (6%)	1/30 (3%)
First incidence (days)	674	736 (T)	666	589
Life table test	P=0.047	P=0.732	P=0.153	P=0.127
Logistic regression test	P=0.071	P=0.762	P=0.182	P=0.187
Cochran-Armitage test	P=0.071			
Fisher exact test		P=0.748N	P=0.181	P=0.175
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	7/51 (14%)	16/50 (32%)	22/49 (45%)
Adjusted rate	9.3%	18.2%	39.4%	54.3%
Terminal rate	3/42 (7%)	5/36 (14%)	11/35 (31%)	12/30 (40%)
First incidence (days)	674	656	666	565
Life table test	P<0.001	P=0.194	P=0.001	P<0.001
Logistic regression test	P<0.001	P=0.233	P=0.003	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.274	P=0.003	P<0.001
Kidney (Renal Tubule): Adenoma				
Overall rate	0/49 (0%)	0/51 (0%)	3/50 (6%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	8.0%	6.7%
Terminal rate	0/42 (0%)	0/36 (0%)	2/35 (6%)	2/30 (7%)
First incidence (days)	—[e]	—	669	736 (T)
Life table test	P=0.060	—	P=0.100	P=0.168
Logistic regression test	P=0.076	—	P=0.120	P=0.168
Cochran-Armitage test	P=0.093			
Fisher exact test		—	P=0.125	P=0.247
Liver: Hepatocellular Adenoma				
Overall rate	18/49 (37%)	20/51 (39%)	19/49 (39%)	19/49 (39%)
Adjusted rate	40.8%	50.8%	48.1%	49.7%
Terminal rate	16/42 (38%)	17/36 (47%)	15/35 (43%)	12/30 (40%)
First incidence (days)	606	461	536	447
Life table test	P=0.137	P=0.224	P=0.271	P=0.147
Logistic regression test	P=0.414	P=0.357	P=0.464	P=0.454
Cochran-Armitage test	P=0.477			
Fisher exact test		P=0.480	P=0.500	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	11/49 (22%)	17/51 (33%)	15/49 (31%)	7/49 (14%)
Adjusted rate	22.7%	39.7%	34.3%	19.3%
Terminal rate	5/42 (12%)	11/36 (31%)	7/35 (20%)	3/30 (10%)
First incidence (days)	478	543	579	515
Life table test	P=0.298N	P=0.094	P=0.183	P=0.414N
Logistic regression test	P=0.032N	P=0.208	P=0.345	P=0.103N
Cochran-Armitage test	P=0.108N			
Fisher exact test		P=0.161	P=0.246	P=0.217N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	27/49 (55%)	32/51 (63%)	27/49 (55%)	23/49 (47%)
Adjusted rate	55.1%	72.4%	60.9%	56.4%
Terminal rate	20/42 (48%)	24/36 (67%)	18/35 (51%)	13/30 (43%)
First incidence (days)	478	461	536	447
Life table test	P=0.448	P=0.090	P=0.314	P=0.381
Logistic regression test	P=0.157N	P=0.225	P=0.506N	P=0.212N
Cochran-Armitage test	P=0.145N			
Fisher exact test		P=0.283	P=0.580N	P=0.272N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	11/49 (22%)	17/51 (33%)	15/49 (31%)	7/49 (14%)
Adjusted rate	22.7%	39.7%	34.3%	19.3%
Terminal rate	5/42 (12%)	11/36 (31%)	7/35 (20%)	3/30 (10%)
First incidence (days)	478	543	579	515
Life table test	P=0.298N	P=0.094	P=0.183	P=0.414N
Logistic regression test	P=0.032N	P=0.208	P=0.345	P=0.103N
Cochran-Armitage test	P=0.108N			
Fisher exact test		P=0.161	P=0.246	P=0.217N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	27/49 (55%)	32/51 (63%)	27/49 (55%)	23/49 (47%)
Adjusted rate	55.1%	72.4%	60.9%	56.4%
Terminal rate	20/42 (48%)	24/36 (67%)	18/35 (51%)	13/30 (43%)
First incidence (days)	478	461	536	447
Life table test	P=0.448	P=0.090	P=0.314	P=0.381
Logistic regression test	P=0.157N	P=0.225	P=0.506N	P=0.212N
Cochran-Armitage test	P=0.145N			
Fisher exact test		P=0.283	P=0.580N	P=0.272N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/50 (24%)	4/51 (8%)	12/50 (24%)	21/49 (43%)
Adjusted rate	27.1%	10.3%	30.6%	57.6%
Terminal rate	10/42 (24%)	3/36 (8%)	9/35 (26%)	15/30 (50%)
First incidence (days)	478	586	536	593
Life table test	P<0.001	P=0.057N	P=0.422	P=0.004
Logistic regression test	P=0.001	P=0.030N	P=0.589	P=0.020
Cochran-Armitage test	P=0.002			
Fisher exact test		P=0.024N	P=0.592N	P=0.037

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/50 (6%)	7/51 (14%)	8/50 (16%)	11/49 (22%)
Adjusted rate	7.1%	18.7%	19.9%	33.5%
Terminal rate	3/42 (7%)	6/36 (17%)	5/35 (14%)	9/30 (30%)
First incidence (days)	736 (T)	646	572	641
Life table test	P=0.004	P=0.108	P=0.068	P=0.004
Logistic regression test	P=0.011	P=0.130	P=0.098	P=0.009
Cochran-Armitage test	P=0.016			
Fisher exact test		P=0.167	P=0.100	P=0.018
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	11/51 (22%)	16/50 (32%)	25/49 (51%)
Adjusted rate	33.9%	28.4%	38.9%	66.9%
Terminal rate	13/42 (31%)	9/36 (25%)	11/35 (31%)	18/30 (60%)
First incidence (days)	478	586	536	593
Life table test	P<0.001	P=0.395N	P=0.315	P=0.002
Logistic regression test	P=0.003	P=0.280N	P=0.491	P=0.011
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.229N	P=0.500	P=0.027
Spleen: Hemangiosarcoma				
Overall rate	0/49 (0%)	3/51 (6%)	0/49 (0%)	0/49 (0%)
Adjusted rate	0.0%	8.3%	0.0%	0.0%
Terminal rate	0/42 (0%)	3/36 (8%)	0/35 (0%)	0/30 (0%)
First incidence (days)	—	736 (T)	—	—
Life table test	P=0.382N	P=0.095	—	—
Logistic regression test	P=0.382N	P=0.095	—	—
Cochran-Armitage test	P=0.314N			
Fisher exact test		P=0.129	—	—
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	3/51 (6%)	2/50 (4%)	2/49 (4%)
Adjusted rate	0.0%	8.0%	5.7%	6.7%
Terminal rate	0/42 (0%)	2/36 (6%)	2/35 (6%)	2/30 (7%)
First incidence (days)	—	683	736 (T)	736 (T)
Life table test	P=0.222	P=0.100	P=0.199	P=0.168
Logistic regression test	P=0.262	P=0.112	P=0.199	P=0.168
Cochran-Armitage test	P=0.314			
Fisher exact test		P=0.125	P=0.247	P=0.242
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	3/51 (6%)	3/50 (6%)	4/49 (8%)
Adjusted rate	0.0%	8.0%	8.6%	12.4%
Terminal rate	0/42 (0%)	2/36 (6%)	3/35 (9%)	3/30 (10%)
First incidence (days)	—	683	736 (T)	669
Life table test	P=0.037	P=0.100	P=0.091	P=0.034
Logistic regression test	P=0.053	P=0.112	P=0.091	P=0.047
Cochran-Armitage test	P=0.071			
Fisher exact test		P=0.125	P=0.121	P=0.056

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/49 (0%)	3/51 (6%)	0/49 (0%)	4/49 (8%)
Adjusted rate	0.0%	8.3%	0.0%	12.4%
Terminal rate	0/42 (0%)	3/36 (8%)	0/35 (0%)	3/30 (10%)
First incidence (days)	—	736 (T)	—	669
Life table test	P=0.035	P=0.095	—	P=0.034
Logistic regression test	P=0.046	P=0.095	—	P=0.047
Cochran-Armitage test	P=0.065			
Fisher exact test		P=0.129	—	P=0.059
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/49 (2%)	3/51 (6%)	0/49 (0%)	4/49 (8%)
Adjusted rate	2.4%	8.3%	0.0%	12.4%
Terminal rate	1/42 (2%)	3/36 (8%)	0/35 (0%)	3/30 (10%)
First incidence (days)	736 (T)	736 (T)	—	669
Life table test	P=0.096	P=0.252	P=0.536N	P=0.104
Logistic regression test	P=0.120	P=0.252	P=0.536N	P=0.138
Cochran-Armitage test	P=0.160			
Fisher exact test		P=0.324	P=0.500N	P=0.181
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	5/51 (10%)	0/50 (0%)	4/49 (8%)
Adjusted rate	4.8%	13.3%	0.0%	13.3%
Terminal rate	2/42 (5%)	4/36 (11%)	0/35 (0%)	4/30 (13%)
First incidence (days)	736 (T)	656	—	736 (T)
Life table test	P=0.296	P=0.165	P=0.279N	P=0.195
Logistic regression test	P=0.351	P=0.191	P=0.279N	P=0.195
Cochran-Armitage test	P=0.424			
Fisher exact test		P=0.226	P=0.247N	P=0.329
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	6/51 (12%)	0/50 (0%)	5/49 (10%)
Adjusted rate	4.8%	16.0%	0.0%	16.7%
Terminal rate	2/42 (5%)	5/36 (14%)	0/35 (0%)	5/30 (17%)
First incidence (days)	736 (T)	656	—	736 (T)
Life table test	P=0.194	P=0.095	P=0.279N	P=0.102
Logistic regression test	P=0.240	P=0.113	P=0.279N	P=0.102
Cochran-Armitage test	P=0.317			
Fisher exact test		P=0.141	P=0.247N	P=0.210
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	2/50 (4%)	3/51 (6%)	6/50 (12%)	4/49 (8%)
Adjusted rate	4.8%	8.3%	15.0%	12.1%
Terminal rate	2/42 (5%)	3/36 (8%)	3/35 (9%)	3/30 (10%)
First incidence (days)	736 (T)	736 (T)	662	592
Life table test	P=0.140	P=0.430	P=0.102	P=0.213
Logistic regression test	P=0.210	P=0.430	P=0.130	P=0.299
Cochran-Armitage test	P=0.234			
Fisher exact test		P=0.509	P=0.134	P=0.329

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign Neoplasms				
Overall rate	30/50 (60%)	30/51 (59%)	38/50 (76%)	43/49 (88%)
Adjusted rate	66.6%	69.3%	84.3%	97.7%
Terminal rate	27/42 (64%)	23/36 (64%)	28/35 (80%)	29/30 (97%)
First incidence (days)	478	362	536	447
Life table test	P<0.001	P=0.276	P=0.011	P<0.001
Logistic regression test	P<0.001	P=0.527	P=0.050	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.533N	P=0.066	P=0.002
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	32/51 (63%)	24/50 (48%)	30/49 (61%)
Adjusted rate	35.2%	67.9%	52.9%	70.9%
Terminal rate	11/42 (26%)	21/36 (58%)	14/35 (40%)	18/30 (60%)
First incidence (days)	478	362	572	447
Life table test	P=0.005	P=0.002	P=0.066	P=0.001
Logistic regression test	P=0.067	P=0.004	P=0.119	P=0.007
Cochran-Armitage test	P=0.026			
Fisher exact test		P=0.003	P=0.111	P=0.006
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/50 (74%)	43/51 (84%)	45/50 (90%)	45/49 (92%)
Adjusted rate	75.5%	87.8%	91.8%	97.8%
Terminal rate	30/42 (71%)	30/36 (83%)	31/35 (89%)	29/30 (97%)
First incidence (days)	478	362	536	447
Life table test	P<0.001	P=0.040	P=0.012	P<0.001
Logistic regression test	P=0.016	P=0.089	P=0.026	P=0.007
Cochran-Armitage test	P=0.011			
Fisher exact test		P=0.151	P=0.033	P=0.017

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for kidney, liver, lung, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Harderian Gland Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	4/50	0/50	4/50
C.I. Pigment Red 23	2/50	0/50	2/50
C.I. Pigment Red 3	2/50	0/50	2/50
Ethylene Glycol	0/54	0/54	0/54
Nitrofurantoin	2/50	0/50	2/50
o-Nitroanisole	9/50	1/50	10/50
p-Nitrobenzoic Acid	1/50	0/50	1/50
Polysorbate 80	0/49	0/49	0/49
Rhodamine 6G	7/50	0/50	7/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	71/1,474 (4.8%)	9/1,474 (0.6%)	80/1,474 (5.4%)
Standard deviation	4.2%	1.1%	4.5%
Range	0%-18%	0%-4%	0%-20%

[a] Data as of 31 March 1993

TABLE C4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	9/50	5/50	14/50
C.I. Pigment Red 23	4/49	2/49	5/49
C.I. Pigment Red 3	2/50	0/50	2/50
Ethylene Glycol	7/54	1/54	7/54
Nitrofurantoin	5/50	1/50	6/50
o-Nitroanisole	5/50	1/50	6/50
p-Nitrobenzoic Acid	6/50	1/50	7/50
Polysorbate 80	5/49	1/49	6/49
Rhodamine 6G	6/50	3/50	9/50
Roxarsone	5/50	6/50	11/50
Overall Historical Incidence			
Total	201/1,469 (13.7%)	73/1,469 (5.0%)	265/1,469 (18.0%)
Standard deviation	6.2%	4.0%	7.6%
Range	4%-28%	0%-14%	4%-32%

[a] Data as of 31 March 1993

TABLE C4c
Historical Incidence of Renal Tubule Adenoma in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/49
C.I. Pigment Red 3	0/50
Ethylene Glycol	1/54
Nitrofurantoin	0/50
o-Nitroanisole	1/50
p-Nitrobenzoic Acid	0/50
Polysorbate 80	0/49
Rhodamine 6G	1/50
Roxarsone	0/50
Overall Historical Incidence	
Total	3/1,466 (0.2%)
Standard deviation	0.6%
Range	0%-2%

[a] Data as of 31 March 1993

TABLE C4d
Historical Incidence of Forestomach Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	3/50	0/50	3/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	0/50	0/50	0/50
Ethylene Glycol	0/54	0/54	0/54
Nitrofurantoin	0/50	1/50	1/50
o-Nitroanisole	3/50	0/50	3/50
p-Nitrobenzoic Acid	0/50	0/50	0/50
Polysorbate 80	1/49	0/49	1/49
Rhodamine 6G	2/50	0/50	2/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	20/1,474 (1.4%)	2/1,474 (0.1%)	22/1,474 (1.5%)
Standard deviation	2.0%	0.5%	2.0%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 31 March 1993

TABLE C4e
Historical Incidence of Hemangioma and Hemangiosarcoma in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Hemangioma	Hemangiosarcoma
Historical Incidence at Southern Research Institute		
Benzyl Acetate	0/50	2/50
C.I. Pigment Red 23	0/50	2/50
C.I. Pigment Red 3	0/50	0/50
Ethylene Glycol	0/54	3/54
Nitrofurantoin	0/50	3/50
o-Nitroanisole	1/50	3/50
p-Nitrobenzoic Acid	0/50	6/50
Polysorbate 80	0/49	0/49
Rhodamine 6G	1/50	1/50
Roxarsone	0/50	3/50
Overall Historical Incidence		
Total	8/1474 (0.54%)	75/1,474 (5.1%)
Standard deviation	1.04	3.9%
Range	0%-3%	0%-16%

[a] Data as of 31 March 1993

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	9	10	10
Early deaths				
Accidental death				1
Moribund	3	12	11	13
Natural deaths	5	3	4	5
Survivors				
Terminal sacrifice	42	36	35	30
Missing				1
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Intestine small, ileum	(10)	(9)	(10)	(10)
Peyer's patch, hyperplasia	1 (10%)			
Liver	(10)	(9)	(10)	(10)
Basophilic focus			1 (10%)	
Clear cell focus				1 (10%)
Inflammation, subacute			1 (10%)	
Mesentery				(1)
Fat, necrosis				1 (100%)
Pancreas	(10)	(9)	(10)	(10)
Atrophy			1 (10%)	
Salivary glands	(10)	(9)	(10)	(10)
Inflammation, chronic			1 (10%)	
Stomach, forestomach	(10)	(9)	(10)	(10)
Mucosa, hyperplasia			1 (10%)	
Cardiovascular System				
Heart	(10)	(9)	(10)	(10)
Inflammation, chronic			1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(9)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)			
Cyst			1 (10%)	
Hyperplasia, focal	1 (10%)	1 (11%)		
Hypertrophy, focal		3 (33%)	1 (10%)	1 (10%)
Islets, pancreatic	(10)	(9)	(10)	(10)
Hyperplasia	3 (30%)	4 (44%)		2 (20%)
Parathyroid gland	(10)	(8)	(9)	(10)
Cyst		1 (13%)	2 (22%)	
Pituitary gland	(9)	(8)	(9)	(8)
Pars distalis, cyst	2 (22%)			
Thyroid gland	(10)	(9)	(10)	(10)
Degeneration, cystic	2 (20%)	1 (11%)	2 (20%)	
Follicle, cyst		1 (11%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Epididymis	(10)	(9)	(10)	(10)
Atypia cellular			1 (10%)	
Hypospermia		1 (11%)	1 (10%)	
Preputial gland	(10)	(9)	(10)	(10)
Ectasia	4 (40%)	5 (56%)	6 (60%)	7 (70%)
Inflammation, chronic	3 (30%)	3 (33%)	2 (20%)	2 (20%)
Testes	(10)	(9)	(10)	(10)
Granuloma sperm		1 (11%)		
Interstitial cell, hyperplasia			1 (10%)	
Seminiferous tubule, atrophy		1 (11%)	1 (10%)	
Hematopoietic System				
Bone marrow	(10)	(9)	(10)	(10)
Hypercellularity	1 (10%)		1 (10%)	
Lymph node				(1)
Bronchial, hyperplasia, lymphoid				1 (100%)
Lymph node, mesenteric	(10)	(9)	(10)	(10)
Hemorrhage	2 (20%)		2 (20%)	
Hyperplasia, lymphoid			1 (10%)	
Spleen	(10)	(9)	(10)	(10)
Hematopoietic cell proliferation	2 (20%)	2 (22%)	1 (10%)	2 (20%)
Integumentary System				
Skin	(10)	(9)	(10)	(10)
Acanthosis		1 (11%)		
Nervous System				
Brain	(10)	(9)	(10)	(10)
Cyst	1 (10%)			
Hemorrhage	1 (10%)			
Respiratory System				
Lung	(10)	(9)	(10)	(10)
Hemorrhage			1 (10%)	
Infiltration cellular, histiocyte				1 (10%)
Alveolar epithelium, hyperplasia	1 (10%)		1 (10%)	3 (30%)
Nose	(10)	(9)	(10)	(10)
Mucosa, hyperplasia				1 (10%)
Special Senses System				
Harderian gland	(4)	(6)	(5)	(4)
Hyperplasia			1 (20%)	1 (25%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(9)	(10)	(10)
Casts protein	1 (10%)	3 (33%)		1 (10%)
Cyst	1 (10%)		2 (20%)	1 (10%)
Hydronephrosis	1 (10%)	1 (11%)		
Mineralization	6 (60%)	6 (67%)	4 (40%)	3 (30%)
Renal tubule, regeneration	7 (70%)	6 (67%)	8 (80%)	8 (80%)
Systems Examined With No Lesions Observed				
General Body System				
Musculoskeletal System				
2-Year Study				
Alimentary System				
Intestine large, colon	(48)	(50)	(49)	(45)
Edema			1 (2%)	
Intestine large, rectum	(48)	(50)	(48)	(48)
Edema			1 (2%)	
Inflammation, chronic			1 (2%)	
Intestine large, cecum	(49)	(49)	(48)	(48)
Edema	3 (6%)	4 (8%)	1 (2%)	8 (17%)
Parasite metazoan		1 (2%)		
Intestine small, jejunum	(49)	(49)	(49)	(48)
Peyer's patch, hyperplasia	1 (2%)			
Intestine small, ileum	(48)	(48)	(47)	(48)
Amyloid deposition		1 (2%)		
Hyperplasia, lymphoid			1 (2%)	
Peyer's patch, hyperplasia	1 (2%)			
Liver	(49)	(51)	(49)	(49)
Basophilic focus	3 (6%)	3 (6%)	3 (6%)	3 (6%)
Clear cell focus	6 (12%)	7 (14%)	3 (6%)	2 (4%)
Congestion		1 (2%)		
Cyst			1 (2%)	
Developmental malformation			1 (2%)	
Eosinophilic focus	4 (8%)	4 (8%)	7 (14%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		4 (8%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, subacute	3 (6%)	2 (4%)	5 (10%)	3 (6%)
Mineralization			2 (4%)	2 (4%)
Mixed cell focus	5 (10%)	2 (4%)	1 (2%)	2 (4%)
Necrosis			1 (2%)	1 (2%)
Thrombosis		1 (2%)		
Hepatocyte, nuclear alteration		1 (2%)	3 (6%)	
Hepatocyte, vacuolization cytoplasmic		1 (2%)		
Kupffer cell, hyperplasia	1 (2%)	2 (4%)	2 (4%)	5 (10%)
Kupffer cell, pigmentation	1 (2%)		2 (4%)	2 (4%)
Lobules, necrosis	1 (2%)	4 (8%)	4 (8%)	3 (6%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(3)	(2)	(1)	(3)
Fat, necrosis	3 (100%)		1 (100%)	1 (33%)
Pancreas	(49)	(51)	(49)	(49)
Atrophy	1 (2%)	1 (2%)		1 (2%)
Cyst	1 (2%)			
Acinar cell, cytoplasmic alteration	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Salivary glands	(49)	(51)	(49)	(49)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic				1 (2%)
Stomach, forestomach	(49)	(51)	(50)	(48)
Diverticulum		1 (2%)		
Ulcer	2 (4%)		1 (2%)	3 (6%)
Mucosa, hyperplasia	4 (8%)	1 (2%)	3 (6%)	4 (8%)
Stomach, glandular	(49)	(51)	(49)	(48)
Ectopic tissue				1 (2%)
Edema		1 (2%)	1 (2%)	
Erosion		1 (2%)	1 (2%)	
Mineralization	1 (2%)			
Mucosa, hyperplasia		2 (4%)		2 (4%)
Tooth	(13)	(2)	(4)	(3)
Dysplasia	13 (100%)	2 (100%)	4 (100%)	3 (100%)
Cardiovascular System				
Heart	(50)	(51)	(50)	(49)
Mineralization			1 (2%)	3 (6%)
Thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(48)	(51)	(50)	(49)
Accessory adrenal cortical nodule	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Hyperplasia, focal	3 (6%)	3 (6%)	7 (14%)	3 (6%)
Hypertrophy, focal	14 (29%)	17 (33%)	16 (32%)	9 (18%)
Vacuolization cytoplasmic		1 (2%)		
Capsule, hyperplasia	5 (10%)	4 (8%)	5 (10%)	5 (10%)
Adrenal medulla	(49)	(50)	(50)	(49)
Hyperplasia	1 (2%)	2 (4%)		
Islets, pancreatic	(49)	(50)	(49)	(49)
Hemorrhage				1 (2%)
Hyperplasia	14 (29%)	12 (24%)	12 (24%)	6 (12%)
Parathyroid gland	(47)	(48)	(47)	(48)
Cyst	2 (4%)	1 (2%)	4 (9%)	1 (2%)
Pituitary gland	(48)	(46)	(50)	(46)
Pars distalis, cyst		3 (7%)	2 (4%)	3 (7%)
Pars distalis, hyperplasia, focal	1 (2%)			
Thyroid gland	(49)	(51)	(49)	(49)
Degeneration, cystic	8 (16%)	8 (16%)	10 (20%)	6 (12%)
Follicle, cyst	2 (4%)	2 (4%)	1 (2%)	
Follicular cell, hyperplasia	6 (12%)	6 (12%)	4 (8%)	2 (4%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
General Body System				
Tissue NOS	(1)			
Cyst	1 (100%)			
Genital System				
Coagulating gland	(2)	(2)		
Dilatation	2 (100%)	2 (100%)		
Epididymis	(49)	(51)	(50)	(49)
Granuloma sperm			1 (2%)	
Hypospermia	1 (2%)			1 (2%)
Inflammation, chronic			1 (2%)	1 (2%)
Spermatocele	1 (2%)	2 (4%)		2 (4%)
Preputial gland	(48)	(49)	(49)	(48)
Angiectasis		1 (2%)	1 (2%)	
Atrophy	2 (4%)		1 (2%)	
Ectasia	24 (50%)	18 (37%)	24 (49%)	21 (44%)
Hyperplasia			1 (2%)	1 (2%)
Inflammation, chronic	22 (46%)	16 (33%)	20 (41%)	12 (25%)
Inflammation, granulomatous				1 (2%)
Inflammation, suppurative	8 (17%)	13 (27%)	15 (31%)	11 (23%)
Prostate	(49)	(51)	(50)	(47)
Hemorrhage			1 (2%)	
Inflammation, suppurative		1 (2%)	1 (2%)	
Seminal vesicle	(49)	(51)	(50)	(49)
Dilatation	15 (31%)	10 (20%)	11 (22%)	8 (16%)
Fibrosis				1 (2%)
Hemorrhage	2 (4%)	1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)		
Testes	(49)	(51)	(50)	(49)
Seminiferous tubule, atrophy	3 (6%)		1 (2%)	2 (4%)
Hematopoietic System				
Bone marrow	(49)	(51)	(50)	(49)
Hypercellularity	4 (8%)	12 (24%)	10 (20%)	13 (27%)
Necrosis		1 (2%)		1 (2%)
Lymph node	(3)	(3)	(5)	(6)
Iliac, hyperplasia, lymphoid		1 (33%)		
Inguinal, hematopoietic cell proliferation				1 (17%)
Inguinal, hyperplasia, lymphoid	2 (67%)	2 (67%)	1 (20%)	3 (50%)
Inguinal, pigmentation	1 (33%)			
Mediastinal, hematopoietic cell proliferation				1 (17%)
Mediastinal, hyperplasia, lymphoid				1 (17%)
Renal, hemorrhage	1 (33%)			
Renal, hyperplasia, lymphoid	1 (33%)			
Lymph node, mandibular	(46)	(49)	(49)	(46)
Atrophy		2 (4%)		
Hematopoietic cell proliferation		1 (2%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	1 (2%)	5 (11%)
Pigmentation	6 (13%)	3 (6%)	6 (12%)	3 (7%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(49)	(49)	(48)
Angiectasis			2 (4%)	2 (4%)
Atrophy		1 (2%)		
Hematopoietic cell proliferation		4 (8%)	3 (6%)	5 (10%)
Hemorrhage	17 (35%)	15 (31%)	16 (33%)	22 (46%)
Hyperplasia, lymphoid	4 (8%)	12 (24%)	7 (14%)	4 (8%)
Pigmentation	1 (2%)	1 (2%)		1 (2%)
Spleen	(49)	(51)	(49)	(49)
Hematopoietic cell proliferation	8 (16%)	20 (39%)	15 (31%)	17 (35%)
Infiltration cellular, mast cell				1 (2%)
Lymphoid follicle, atrophy	1 (2%)	4 (8%)		1 (2%)
Lymphoid follicle, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Red pulp, atrophy		2 (4%)		1 (2%)
Thymus	(44)	(48)	(40)	(42)
Atrophy		4 (8%)		4 (10%)
Congestion		1 (2%)		
Hyperplasia, lymphoid	1 (2%)			
Integumentary System				
Skin	(50)	(51)	(50)	(49)
Acanthosis			2 (4%)	
Cyst epithelial inclusion			1 (2%)	
Inflammation, subacute			1 (2%)	
Inflammation, suppurative		1 (2%)	1 (2%)	
Ulcer		1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(51)	(50)	(49)
Hyperostosis		2 (4%)		3 (6%)
Nervous System				
Brain	(50)	(51)	(50)	(49)
Compression				1 (2%)
Cyst			1 (2%)	1 (2%)
Hemorrhage		1 (2%)		
Necrosis		1 (2%)		
Respiratory System				
Lung	(50)	(51)	(50)	(49)
Congestion		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid	3 (6%)		1 (2%)	1 (2%)
Infiltration cellular, histiocyte	6 (12%)	8 (16%)	5 (10%)	9 (18%)
Inflammation, subacute		1 (2%)		
Thrombosis	1 (2%)		1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia	6 (12%)	7 (14%)	5 (10%)	8 (16%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(49)	(51)	(50)	(49)
Exudate	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Foreign body	1 (2%)			
Special Senses System				
Eye		(2)	(4)	(9)
Cataract		1 (50%)	1 (25%)	2 (22%)
Inflammation, chronic		1 (50%)	3 (75%)	2 (22%)
Phthisis bulbi		1 (50%)		
Cornea, hyperplasia			1 (25%)	
Harderian gland	(22)	(25)	(28)	(32)
Hyperplasia		1 (4%)	1 (4%)	2 (6%)
Urinary System				
Kidney	(49)	(51)	(50)	(49)
Casts protein	6 (12%)	11 (22%)	10 (20%)	4 (8%)
Cyst	12 (24%)	13 (25%)	8 (16%)	11 (22%)
Hydronephrosis		3 (6%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)	
Metaplasia, osseous	1 (2%)	1 (2%)	2 (4%)	
Mineralization	35 (71%)	29 (57%)	37 (74%)	30 (61%)
Papilla, necrosis		1 (2%)		
Renal tubule, atrophy	1 (2%)		1 (2%)	2 (4%)
Renal tubule, casts protein		1 (2%)		
Renal tubule, dilatation	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Renal tubule, hyperplasia				2 (4%)
Renal tubule, necrosis	1 (2%)	1 (2%)		
Renal tubule, pigmentation			1 (2%)	
Renal tubule, regeneration	43 (88%)	41 (80%)	45 (90%)	36 (73%)
Transitional epithelium, hyperplasia		1 (2%)		
Urethra	(1)			
Concretion	1 (100%)			
Inflammation, subacute	1 (100%)			
Urinary bladder	(49)	(51)	(49)	(49)
Dilatation	2 (4%)			
Edema		1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, suppurative		1 (2%)		
Mucosa, hyperplasia		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	8	10	9	10
Early deaths				
Moribund	9	14	14	29
Natural deaths	6	6	11	10
Survivors				
Terminal sacrifice	37	30	26	11
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(8)	(10)	(9)	(10)
Hemangioma			1 (11%)	
Liver	(8)	(10)	(9)	(10)
Hepatocellular adenoma				1 (10%)
Hepatocellular adenoma, multiple			1 (11%)	
Stomach, forestomach	(8)	(10)	(9)	(10)
Squamous cell papilloma				1 (10%)
Endocrine System				
Pituitary gland	(8)	(10)	(9)	(10)
Pars distalis, adenoma			1 (11%)	
Genital System				
Vagina				(1)
Squamous cell papilloma				1 (100%)
Respiratory System				
Lung	(8)	(10)	(9)	(10)
Alveolar/bronchiolar adenoma	1 (13%)			2 (20%)
Alveolar/bronchiolar carcinoma	1 (13%)			
Special Senses System				
Harderian gland	(4)	(5)	(4)	(7)
Adenoma	1 (25%)	1 (20%)		4 (57%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Hematopoetic System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(49)	(47)	(47)	(45)
Sarcoma, metastatic, mesentery				1 (2%)
Intestine large, colon	(52)	(50)	(49)	(49)
Hemangioma				1 (2%)
Intestine large, rectum	(50)	(50)	(51)	(50)
Histiocytic sarcoma				1 (2%)
Intestine large, cecum	(52)	(50)	(49)	(50)
Intestine small, jejunum	(49)	(49)	(49)	(47)
Liver	(51)	(50)	(50)	(49)
Hepatocellular carcinoma	4 (8%)	8 (16%)	5 (10%)	1 (2%)
Hepatocellular carcinoma, multiple	1 (2%)			2 (4%)
Hepatocellular adenoma	13 (25%)	9 (18%)	4 (8%)	13 (27%)
Hepatocellular adenoma, multiple	3 (6%)	3 (6%)	1 (2%)	3 (6%)
Histiocytic sarcoma		2 (4%)	2 (4%)	1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Mesentery	(4)	(6)	(7)	(6)
Sarcoma				1 (17%)
Yolk sac carcinoma, metastatic, ovary			1 (14%)	
Pancreas	(51)	(50)	(49)	(48)
Sarcoma, metastatic, mesentery				1 (2%)
Sarcoma stromal, metastatic, uterus		1 (2%)		
Salivary glands	(52)	(50)	(51)	(50)
Stomach, forestomach	(51)	(50)	(51)	(49)
Squamous cell papilloma		1 (2%)	5 (10%)	3 (6%)
Stomach, glandular	(51)	(50)	(49)	(49)
Sarcoma stromal, metastatic, uterus		1 (2%)		
Tongue		(1)		
Squamous cell carcinoma		1 (100%)		
Cardiovascular System				
Heart	(52)	(50)	(51)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(51)	(50)	(51)	(49)
Sarcoma, metastatic, skin				1 (2%)
Capsule, carcinoma		1 (2%)		
Adrenal medulla	(51)	(50)	(51)	(49)
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(51)	(50)	(49)	(49)
Adenoma	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Pituitary gland	(50)	(48)	(48)	(46)
Pars distalis, adenoma	4 (8%)	8 (17%)	2 (4%)	5 (11%)
Pars distalis, carcinoma			1 (2%)	
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(51)	(50)	(51)	(50)
Follicular cell, adenoma	3 (6%)	1 (2%)	3 (6%)	
General Body System				
Tissue NOS		(2)		
Genital System				
Ovary	(51)	(49)	(51)	(48)
Adenoma	1 (2%)		1 (2%)	
Carcinoma				1 (2%)
Granulosa cell tumor benign			1 (2%)	1 (2%)
Luteoma			2 (4%)	
Yolk sac carcinoma			1 (2%)	
Bilateral, adenoma	1 (2%)			
Uterus	(52)	(50)	(51)	(50)
Carcinoma		1 (2%)	2 (4%)	2 (4%)
Deciduoma benign		1 (2%)		
Hemangioma		1 (2%)		
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	
Polyp adenomatous		1 (2%)		
Polyp stromal	3 (6%)	1 (2%)		1 (2%)
Sarcoma stromal		1 (2%)		2 (4%)
Hematopoietic System				
Bone marrow	(52)	(50)	(51)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node	(9)	(12)	(6)	(9)
Mediastinal, sarcoma, metastatic, skin			1 (17%)	
Renal, histiocytic sarcoma		1 (8%)		
Renal, sarcoma, metastatic, skin				1 (11%)
Lymph node, mandibular	(48)	(46)	(50)	(46)
Carcinoma, metastatic, harderian gland	1 (2%)			
Histiocytic sarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(49)	(48)	(46)	(48)
Histiocytic sarcoma		3 (6%)	2 (4%)	1 (2%)
Sarcoma stromal, metastatic, uterus		1 (2%)		
Spleen	(51)	(50)	(50)	(50)
Hemangioma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Thymus	(46)	(47)	(46)	(42)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery				1 (2%)
Integumentary System				
Mammary gland	(52)	(50)	(50)	(49)
Adenoacanthoma				1 (2%)
Carcinoma			1 (2%)	2 (4%)
Carcinoma, multiple				1 (2%)
Skin	(52)	(50)	(51)	(50)
Squamous cell papilloma		1 (2%)		1 (2%)
Sebaceous gland, carcinoma	1 (2%)			
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, fibrous histiocytoma		1 (2%)		
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma				2 (4%)
Subcutaneous tissue, sarcoma			4 (8%)	11 (22%)
Subcutaneous tissue, sarcoma, multiple		1 (2%)		
Subcutaneous tissue, schwannoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(52)	(50)	(51)	(50)
Osteosarcoma	1 (2%)		1 (2%)	1 (2%)
Nervous System				
Peripheral nerve	(1)	(1)	(1)	(1)
Respiratory System				
Lung	(52)	(50)	(51)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	7 (14%)	15 (30%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	2 (4%)	5 (10%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Carcinoma, metastatic, mammary gland				1 (2%)
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (4%)	1 (2%)	
Histiocytic sarcoma		2 (4%)	2 (4%)	1 (2%)
Sarcoma, metastatic, skin			1 (2%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Special Senses System				
Harderian gland	(18)	(27)	(27)	(33)
Adenoma	2 (11%)	6 (22%)	8 (30%)	14 (42%)
Carcinoma	1 (6%)	6 (22%)	5 (19%)	7 (21%)
Bilateral, adenoma				1 (3%)
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(51)	(50)	(51)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Urinary bladder	(51)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(52)	(50)	(51)	(50)
Histiocytic sarcoma	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic	2 (4%)		1 (2%)	1 (2%)
Lymphoma malignant mixed	3 (6%)	7 (14%)	7 (14%)	3 (6%)
Lymphoma malignant undifferentiated cell		3 (6%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	3	1	3	7
2-Year study	35	42	43	42
Total primary neoplasms				
15-Month interim evaluation	3	1	3	9
2-Year study	51	79	75	111
Total animals with benign neoplasms				
15-Month interim evaluation	2	1	3	7
2-Year study	26	29	28	34
Total benign neoplasms				
15-Month interim evaluation	2	1	3	9
2-Year study	35	42	38	63
Total animals with malignant neoplasms				
15-Month interim evaluation	1			
2-Year study	16	32	31	36
Total malignant neoplasms				
15-Month interim evaluation	1			
2-Year study	16	37	37	48
Total animals with metastatic neoplasms				
2-Year study	3	6	7	4
Total metastatic neoplasms				
2-Year study	4	8	8	9

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm

Number of Days on Study	2 8 5	4 0 7	4 4 7	4 8 4	4 9 9	5 6 9	5 7 1	6 1 8	6 2 4	6 3 1	6 3 1	6 4 0	6 4 6	6 4 8	7 0 5	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	2 9 4	2 9 8	2 8 3	2 5 8	2 7 4	2 5 4	2 6 5	2 8 6	2 9 0	2 4 2	2 5 5	2 6 6	2 6 7	2 6 1	2 5 6	2 4 1	2 4 3	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 4 9	2 5 0	2 5 1	2 5 2
Alimentary System																										
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder*	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																										
Hepatocellular carcinoma, multiple																										
Hepatocellular adenoma						X			X	X								X					X			X
Hepatocellular adenoma, multiple																								X		
Mesentery																										
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																				
Parathyroid gland	M	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pituitary gland	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X	X			
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																										
Bilateral, adenoma																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X			
Polyp stromal																								X		

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	2 5 3	2 5 7	2 5 9	2 6 0	2 6 2	2 6 3	2 6 4	2 6 8	2 6 9	2 7 0	2 7 1	2 7 2	2 7 3	2 7 5	2 7 6	2 7 7	2 7 8	2 7 9	2 8 0	2 8 1	2 8 2	2 8 4	2 8 5	2 8 7	2 8 8	2 8 9	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma		X				X	X			X																	4
Hepatocellular carcinoma, multiple													X														1
Hepatocellular adenoma							X				X	X						X	X						X	X	13
Hepatocellular adenoma, multiple																					X	X					3
Mesentery	+			+									+						+								4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																											
Blood vessel													+														1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																											1
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X														X											4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma																		X		X					X		3
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																										1
Bilateral, adenoma																						X					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											1
Polyp stromal			X															X									3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	2 8 5	4 0 7	4 4 7	4 8 4	4 9 9	5 6 9	5 7 1	6 1 8	6 2 4	6 3 1	6 3 1	6 4 0	6 4 6	6 4 8	7 0 5	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	2 9 4	2 9 8	2 8 3	2 5 8	2 7 4	2 5 4	2 6 5	2 8 6	2 9 0	2 4 2	2 5 5	2 6 6	2 6 7	2 6 1	2 5 6	2 4 1	2 4 3	2 4 4	2 4 5	2 4 6	2 4 7	2 4 8	2 4 9	2 5 0	2 5 1	2 5 2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					X					
Lymph node	+			+			+			+	+		+	+	+											
Lymph node, bronchial											+															
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland													X													
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal													+		+											
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, carcinoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma					X																					
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																				
Spinal cord						+																				
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar adenoma, multiple												X														
Alveolar/bronchiolar carcinoma															X											
Carcinoma, metastatic, harderian gland													X													
Hepatocellular carcinoma, metastatic, liver																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland	+	+	+								+		+	+	+			+		+				+		
Adenoma			X								X															
Carcinoma													X													
Urinary System																										
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X			
Lymphoma malignant lymphocytic	X																									
Lymphoma malignant mixed																								X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 0 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	2 5 3	2 5 7	2 5 9	2 6 0	2 6 2	2 6 3	2 6 4	2 6 8	2 6 9	2 7 0	2 7 1	2 7 2	2 7 3	2 7 5	2 7 6	2 7 7	2 7 8	2 7 9	2 8 0	2 8 1	2 8 2	2 8 4	2 8 5	2 8 7	2 8 8	2 8 9	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangioma																											1
Lymph node																+											9
Lymph node, bronchial																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	48
Carcinoma, metastatic, harderian gland																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal																											2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sebaceous gland, carcinoma									X																		1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Osteosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Peripheral nerve																											1
Spinal cord																			+		+						3
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma															X						X						2
Alveolar/bronchiolar adenoma, multiple																											1
Alveolar/bronchiolar carcinoma					X																						2
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver		X					X																				2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Harderian gland		+	+			+											+		+			+	+		+		18
Adenoma																											2
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic																		X									2
Lymphoma malignant mixed	X															X											3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm

Number of Days on Study	0	3	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	8	1	7	0	0	0	1	2	2	3	5	6	6	7	7	7	9	9	3	4	4	4	4
	1	6	3	9	6	6	8	9	5	7	5	5	8	9	0	7	7	2	6	0	3	3	3	3
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	0	1	2	1	4	4	3	3	3	0	1	0	1	2	1	2	0	3	2	0	0	0	0
	1	4	7	1	1	8	0	2	5	8	8	6	2	3	4	0	6	3	6	0	1	5	6	7
Alimentary System																								
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X	X								X	X	X		X							
Hepatocellular adenoma										X						X						X		X
Hepatocellular adenoma, multiple																								
Histiocytic sarcoma				X																				
Mesentery			+									+			+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																						X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																						X		
Tongue						+																		
Squamous cell carcinoma						X																		
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma																								X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X									X		X				X	
Pars intermedia, adenoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
Tissue NOS							+		+															
Genital System																								
Clitoral gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 1 2	3 1 4	3 1 5	3 1 8	3 1 9	3 2 2	3 2 3	3 2 5	3 2 7	3 2 8	3 2 9	3 3 0	3 3 3	3 3 4	3 3 7	3 3 9	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	3 4 6	3 4 7	3 4 9	3 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma				X														X								8
Hepatocellular adenoma			X	X													X							X	X	9
Hepatocellular adenoma, multiple		X						X				X														3
Histiocytic sarcoma			X																							2
Mesentery								+		+									+							6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X				X					X															3
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Pars distalis, adenoma				X					X									X				X				8
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma															X											1
General Body System																										
Tissue NOS																										2
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	0	3	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	8	1	7	0	0	0	1	2	2	3	5	6	6	7	7	7	9	9	3	4	4	4	4
	1	6	3	9	6	6	8	9	5	7	5	5	8	9	0	7	7	2	6	0	3	3	3	3
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	0	1	2	1	4	4	3	3	3	0	1	0	1	2	1	2	0	3	2	0	0	0	0
	1	4	7	1	1	8	0	2	5	8	8	6	2	3	4	0	6	3	6	0	1	5	6	7	9
Genital System (continued)																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X		
Deciduoma benign																								X
Hemangioma											X													
Histiocytic sarcoma				X																				
Polyp adenomatous																								
Polyp stromal																								
Sarcoma stromal																							X	
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Lymph node		+	+				+	+	+				+						+	+			+	
Renal, histiocytic sarcoma																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Sarcoma stromal, metastatic, uterus																							X	
Lymph node, mediastinal		+	+				+		+															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma																				X				
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Subcutaneous tissue, fibrous histiocytoma																	X							
Subcutaneous tissue, hemangioma																				X				
Subcutaneous tissue, sarcoma, multiple																			X					
Subcutaneous tissue, schwannoma malignant												X												
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																					
Spinal cord			+																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 1 2	3 1 4	3 1 5	3 1 8	3 1 9	3 2 2	3 2 3	3 2 5	3 2 7	3 2 8	3 2 9	3 3 0	3 3 3	3 3 4	3 3 7	3 3 9	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	3 4 6	3 4 7	3 4 9	3 5 0	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Deciduoma benign																										1
Hemangioma																										1
Histiocytic sarcoma																										1
Polyp adenomatous																			X							1
Polyp stromal																					X					1
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node													+						+				+			12
Renal, histiocytic sarcoma													X													1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma													X													1
Lymph node, mesenteric	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma			X										X													3
Sarcoma stromal, metastatic, uterus																										1
Lymph node, mediastinal																			+				+			6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																									X	1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, sarcoma, multiple																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	0	3	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7
	0	8	1	7	0	0	0	1	2	2	3	5	6	6	7	7	7	9	9	3	4	4	4	4	4
	1	6	3	9	6	6	8	9	5	7	5	5	8	9	0	7	7	2	6	0	3	3	3	3	3
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	0	1	2	1	4	4	3	3	3	0	1	0	1	2	1	2	0	3	2	0	0	0	0	0
	1	4	7	1	1	8	0	2	5	8	8	6	2	3	4	0	6	3	6	0	1	5	6	7	9
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Alveolar/bronchiolar carcinoma																						X			
Carcinoma, metastatic, harderian gland											X													X	
Carcinoma, metastatic, adrenal cortex																									X
Hepatocellular carcinoma, metastatic, liver					X								X												
Histiocytic sarcoma				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																								+	
Harderian gland							+			+	+	+		+	+		+	+	+	+	+	+		+	+
Adenoma														X			X			X					X
Carcinoma										X	X											X		X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																X					
Lymphoma malignant mixed		X					X		X														X		
Lymphoma malignant undifferentiated cell type			X					X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 312 ppm (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 1 2	3 1 4	3 1 5	3 1 8	3 1 9	3 2 2	3 2 3	3 2 5	3 2 7	3 2 8	3 2 9	3 3 0	3 3 3	3 3 4	3 3 7	3 3 9	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	3 4 6	3 4 7	3 4 9	3 5 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X																					3
Alveolar/bronchiolar carcinoma												X														2
Carcinoma, metastatic, harderian gland																										2
Carcinoma, metastatic, adrenal cortex																										1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma			X																							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																							+			2
Harderian gland	+			+	+	+	+	+	+	+		+			+			+			+		+			27
Adenoma	X					X																				6
Carcinoma															X								X			6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			X										X													4
Lymphoma malignant mixed																	X		X				X			7
Lymphoma malignant undifferentiated cell type									X																	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm

Number of Days on Study	3 9 7	4 2 8	5 3 6	5 4 3	5 5 7	5 7 5	6 0 5	6 2 0	6 2 9	6 3 9	6 3 9	6 5 2	6 6 9	6 6 9	6 6 9	6 7 9	6 8 3	6 9 3	7 0 7	7 0 9	7 1 1	7 1 8	7 1 9	7 2 6	7 3 3
Carcass ID Number	3 8 5	4 1 3	4 0 9	3 7 3	3 9 5	3 7 8	3 6 7	3 6 9	3 9 3	3 6 5	3 9 7	4 0 3	3 6 1	3 8 7	3 9 6	4 0 0	3 9 4	3 6 4	3 9 8	3 8 1	3 7 9	3 8 8	3 6 2	3 7 6	4 0 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X																				
Hepatocellular adenoma																			X						
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																								X	
Mesentery	+								+						+			+							
Yolk sac carcinoma, metastatic, ovary	X																								
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X													X	
Stomach, glandular	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																			X				X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																				X					
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Granulosa cell tumor benign														X											
Luteoma																									
Yolk sac carcinoma	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Histiocytic sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 6 3	3 6 6	3 6 8	3 7 0	3 7 1	3 7 2	3 7 4	3 7 5	3 7 7	3 8 0	3 8 2	3 8 3	3 8 4	3 8 6	3 8 9	3 9 0	3 9 1	3 9 2	3 9 9	4 0 1	4 0 4	4 0 5	4 0 6	4 0 7	4 0 8	4 1 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma															X			X			X		X			5
Hepatocellular adenoma		X																			X			X		4
Hepatocellular adenoma, multiple											X															1
Histiocytic sarcoma							X																			2
Mesentery				+							+					+										7
Yolk sac carcinoma, metastatic, ovary																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma								X														X			X	5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X		X																							2
Pars distalis, carcinoma															X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell, adenoma						X																		X		3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																						X				1
Granulosa cell tumor benign																										1
Luteoma												X						X								2
Yolk sac carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma								X														X				2
Histiocytic sarcoma							X																			1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	3 9 7	4 2 8	5 3 6	5 4 3	5 5 7	5 7 5	6 0 5	6 2 0	6 2 9	6 3 9	6 3 9	6 5 2	6 6 9	6 6 9	6 6 9	6 7 9	6 8 3	6 9 3	7 0 7	7 0 9	7 1 1	7 1 8	7 1 9	7 2 6	7 3 3
Carcass ID Number	3 8 5	4 1 3	4 0 9	3 7 3	3 9 5	3 7 8	3 6 7	3 6 9	3 9 3	3 6 5	3 9 7	4 0 3	3 6 1	3 8 7	3 9 6	4 0 0	3 9 4	3 6 4	3 9 8	3 8 1	3 7 9	3 8 8	3 6 2	3 7 6	4 0 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node								+		+			+					+			+	+			
Mediastinal, sarcoma, metastatic, skin													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	A	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Lymph node, mediastinal								+			+		+					+				+			
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	I	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma			X										X						X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle																			+						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve									+														M		
Spinal cord									+														+		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X									X		X
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma						X											X								
Alveolar/bronchiolar carcinoma, multiple		X																							
Carcinoma, metastatic, harderian gland														X	X										
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																								X	
Sarcoma, metastatic, skin													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Harderian gland	+				+	+	+		+	+			+	+	+				+		+			+	+
Adenoma					X	X			X															X	
Carcinoma														X	X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 6 3	3 6 6	3 6 8	3 7 0	3 7 1	3 7 2	3 7 4	3 7 5	3 7 7	3 8 0	3 8 2	3 8 3	3 8 4	3 8 6	3 8 9	3 9 0	3 9 1	3 9 2	3 9 9	4 0 1	4 0 4	4 0 5	4 0 6	4 0 7	4 0 8	4 1 0	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma							X																				1
Lymph node																											6
Mediastinal, sarcoma, metastatic, skin																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma							X																				2
Lymph node, mediastinal																											5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, sarcoma																										X	4
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Osteosarcoma				X																							1
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Peripheral nerve																											1
Spinal cord					+																						3
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma											X		X							X			X				7
Alveolar/bronchiolar adenoma, multiple																										X	2
Alveolar/bronchiolar carcinoma						X											X	X									5
Alveolar/bronchiolar carcinoma, multiple																											1
Carcinoma, metastatic, harderian gland																	X										3
Hepatocellular carcinoma, metastatic, liver																						X					1
Histiocytic sarcoma							X																				2
Sarcoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																											
Eye					+		+																				3
Harderian gland			+	+	+	+	+	+				+		+		+	+		+		+	+			+		27
Adenoma					X			X													X	X					8
Carcinoma			X				X										X										5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	3	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7
	9	2	3	4	5	7	0	2	2	3	3	5	6	6	6	7	8	9	0	0	1	1	1	2	3
	7	8	6	3	7	5	5	0	9	9	9	2	9	9	9	9	3	3	7	9	1	8	9	6	3
Carcass ID Number	3	4	4	3	3	3	3	3	3	3	3	4	3	3	3	4	3	3	3	3	3	3	3	3	4
	8	1	0	7	9	7	6	6	9	6	9	0	6	8	9	0	9	6	9	8	7	8	6	7	0
	5	3	9	3	5	8	7	9	3	5	7	3	1	7	6	0	4	4	8	1	9	8	2	6	2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								X	
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant mixed										X												X			
Lymphoma malignant undifferentiated cell type																		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 625 ppm (continued)

Number of Days on Study	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 6 3	3 6 6	3 6 8	3 7 0	3 7 1	3 7 2	3 7 4	3 7 5	3 7 7	3 8 0	3 8 2	3 8 3	3 8 4	3 8 6	3 8 9	3 9 0	3 9 1	3 9 2	3 9 9	4 0 1	4 0 4	4 0 5	4 0 6	4 0 7	4 0 8	4 1 0	Total Tissues/ Tumors
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma							X																				2
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed		X			X						X				X					X							7
Lymphoma malignant undifferentiated cell type																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm

Number of Days on Study	4 0 1	4 4 9	4 5 6	4 8 0	4 8 3	4 9 0	5 0 2	5 2 0	5 2 6	5 3 4	5 3 4	5 3 7	5 3 7	5 5 1	5 5 1	5 5 4	5 7 5	5 7 6	5 8 6	6 0 6	6 1 0	6 1 5	6 4 2	6 4 9	6 4 9
Carcass ID Number	4 6 4	4 2 2	4 4 0	4 6 2	4 4 1	4 4 5	4 5 7	4 4 2	4 6 0	4 3 7	4 3 8	4 2 4	4 4 7	4 4 9	4 6 1	4 3 5	4 2 5	4 2 7	4 6 3	4 2 6	4 2 9	4 6 5	4 3 4	4 5 5	4 6 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Gallbladder	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Sarcoma, metastatic, mesentery																									
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																							X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma				X									X	X										X	X
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																					X				
Sarcoma, metastatic, mesentery																									
Mesentery										+				+		+				+					
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Sarcoma, metastatic, mesentery																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin															X										
Adrenal medulla	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	I	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma												X			X		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	45
Sarcoma, metastatic, mesentery											X															1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma		X																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Hepatocellular carcinoma, multiple														X											X	2
Hepatocellular adenoma	X			X	X										X		X					X	X		X	13
Hepatocellular adenoma, multiple								X								X			X							3
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery											X															1
Mesentery											+				+											6
Sarcoma											X															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, mesentery											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma												X									X	X				3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X												X								2
Parathyroid gland	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma											X										X					5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	4 0 1	4 4 9	4 5 6	4 8 0	4 8 3	4 9 0	5 0 2	5 2 0	5 2 6	5 3 4	5 3 4	5 3 7	5 3 7	5 5 1	5 5 1	5 5 4	5 7 5	5 7 6	5 8 6	6 0 6	6 1 0	6 1 5	6 4 2	6 4 9	6 4 9
Carcass ID Number	4 6 4	4 2 2	4 4 0	4 6 2	4 4 1	4 4 5	4 5 7	4 4 2	4 6 0	4 3 7	4 3 8	4 2 4	4 4 7	4 4 9	4 6 1	4 3 5	4 2 5	4 2 7	4 6 3	4 2 6	4 2 9	4 6 5	4 3 4	4 5 5	4 6 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Hemangiosarcoma																									
Polyp stromal																									
Sarcoma stromal																						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+								+				+		+		+	+						+	
Renal, sarcoma, metastatic, skin															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymph node, mediastinal	+																+							+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	M	+	+	+	+
Sarcoma, metastatic, mesentery																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma			X																						
Carcinoma								X																X	
Carcinoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma				X						X		X			X					X			X	X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X														
Skeletal muscle				+								+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord																			+						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma		X																								1
Granulosa cell tumor benign			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								2
Hemangiosarcoma										X																1
Polyp stromal														X												1
Sarcoma stromal													X													2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Lymph node															+		+									9
Renal, sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mediastinal																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Thymus	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	42
Sarcoma, metastatic, mesentery											X															1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adenoacanthoma																										1
Carcinoma																										2
Carcinoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									1
Subcutaneous tissue, fibrosarcoma													X													1
Subcutaneous tissue, hemangiosarcoma												X											X			2
Subcutaneous tissue, sarcoma	X				X									X								X				11
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
	0	4	5	8	8	9	0	2	2	3	3	3	3	5	5	5	7	7	8	0	1	1	4	4
	1	9	6	0	3	0	2	0	6	4	4	7	7	1	1	4	5	6	6	6	0	5	2	9	9
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	6	2	4	6	4	4	5	4	6	3	3	2	4	4	6	3	2	2	6	2	2	6	3	5	6
	4	2	0	2	1	5	7	2	0	7	8	4	7	9	1	5	5	7	3	6	9	5	4	5	7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X	X	X									X		X	X
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland																									
Carcinoma, metastatic, mammary gland																		X							
Histiocytic sarcoma																					X				
Sarcoma, metastatic, skin															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+										+	
Harderian gland	+	+				+		+					+	+		+	+	+	+	+		+	+	+	+
Adenoma														X			X		X	X			X	X	X
Carcinoma																	X			X					X
Bilateral, adenoma																						X			
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X	X							X	X	X				X		X			X				15
Alveolar/bronchiolar adenoma, multiple															X											2
Alveolar/bronchiolar carcinoma				X									X						X				X			4
Alveolar/bronchiolar carcinoma, multiple														X												1
Carcinoma, metastatic, harderian gland								X																		1
Carcinoma, metastatic, mammary gland																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+		+	+		+										+							7
Harderian gland	+		+	+	+	+	+	+	+		+		+		+	+	+		+		+	+	+		+	33
Adenoma				X	X				X				X			X			X				X			14
Carcinoma	X					X	X	X																		7
Bilateral, adenoma																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																	X			X	X					3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	2/52 (4%)	6/50 (12%)	8/51 (16%)	15/50 (30%)
Adjusted rate[b]	4.3%	17.7%	23.7%	55.7%
Terminal rate[c]	0/37 (0%)	3/30 (10%)	4/26 (15%)	3/11 (27%)
First incidence (days)	447	669	557	551
Life table test[d]	P<0.001	P=0.105	P=0.030	P<0.001
Logistic regression test[d]	P<0.001	P=0.125	P=0.040	P<0.001
Cochran-Armitage test[d]	P<0.001			
Fisher exact test[d]		P=0.122	P=0.043	P<0.001
Harderian Gland: Carcinoma				
Overall rate	1/52 (2%)	6/50 (12%)	5/51 (10%)	7/50 (14%)
Adjusted rate	2.5%	17.6%	16.1%	25.0%
Terminal rate	0/37 (0%)	4/30 (13%)	3/26 (12%)	0/11 (0%)
First incidence (days)	646	627	669	575
Life table test	P=0.002	P=0.043	P=0.073	P=0.007
Logistic regression test	P=0.095	P=0.052	P=0.098	P=0.033
Cochran-Armitage test	P=0.051			
Fisher exact test		P=0.050	P=0.098	P=0.026
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/52 (6%)	12/50 (24%)	13/51 (25%)	19/50 (38%)
Adjusted rate	6.7%	33.3%	37.5%	64.2%
Terminal rate	0/37 (0%)	7/30 (23%)	7/26 (27%)	3/11 (27%)
First incidence (days)	447	627	557	551
Life table test	P<0.001	P=0.009	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.010	P=0.006	P=0.002
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.009	P=0.006	P<0.001
Liver: Hepatocellular Adenoma				
Overall rate	16/51 (31%)	12/50 (24%)	5/50 (10%)	16/49 (33%)
Adjusted rate	39.4%	36.8%	17.9%	74.1%
Terminal rate	13/37 (35%)	10/30 (33%)	4/26 (15%)	7/11 (64%)
First incidence (days)	569	627	707	480
Life table test	P=0.004	P=0.458N	P=0.042N	P=0.004
Logistic regression test	P=0.181	P=0.305N	P=0.010N	P=0.197
Cochran-Armitage test	P=0.490			
Fisher exact test		P=0.273N	P=0.007N	P=0.531
Liver: Hepatocellular Carcinoma				
Overall rate	5/51 (10%)	8/50 (16%)	5/50 (10%)	3/49 (6%)
Adjusted rate	13.5%	20.2%	17.2%	19.6%
Terminal rate	5/37 (14%)	2/30 (7%)	4/26 (15%)	1/11 (9%)
First incidence (days)	743 (T)	579	557	642
Life table test	P=0.411	P=0.211	P=0.423	P=0.345
Logistic regression test	P=0.314N	P=0.258	P=0.588	P=0.522
Cochran-Armitage test	P=0.202N			
Fisher exact test		P=0.264	P=0.617	P=0.380N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	20/51 (39%)	19/50 (38%)	9/50 (18%)	18/49 (37%)
Adjusted rate	49.5%	48.7%	30.6%	77.1%
Terminal rate	17/37 (46%)	11/30 (37%)	7/26 (27%)	7/11 (64%)
First incidence (days)	569	579	557	480
Life table test	P=0.010	P=0.415	P=0.098N	P=0.003
Logistic regression test	P=0.418	P=0.563N	P=0.019N	P=0.227
Cochran-Armitage test	P=0.335N			
Fisher exact test		P=0.531N	P=0.016N	P=0.480N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/52 (6%)	3/50 (6%)	9/51 (18%)	17/50 (34%)
Adjusted rate	7.7%	8.8%	29.1%	64.2%
Terminal rate	2/37 (5%)	2/30 (7%)	5/26 (19%)	4/11 (36%)
First incidence (days)	640	619	669	534
Life table test	P<0.001	P=0.590	P=0.024	P<0.001
Logistic regression test	P<0.001	P=0.642	P=0.048	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.642	P=0.057	P<0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/52 (4%)	2/50 (4%)	6/51 (12%)	5/50 (10%)
Adjusted rate	5.3%	6.7%	17.6%	33.9%
Terminal rate	1/37 (3%)	2/30 (7%)	3/26 (12%)	2/11 (18%)
First incidence (days)	705	743 (T)	428	669
Life table test	P=0.003	P=0.617	P=0.085	P=0.009
Logistic regression test	P=0.048	P=0.659	P=0.125	P=0.094
Cochran-Armitage test	P=0.102			
Fisher exact test		P=0.676	P=0.128	P=0.202
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/52 (10%)	5/50 (10%)	15/51 (29%)	19/50 (38%)
Adjusted rate	12.7%	15.3%	43.4%	71.9%
Terminal rate	3/37 (8%)	4/30 (13%)	8/26 (31%)	5/11 (45%)
First incidence (days)	640	619	428	534
Life table test	P<0.001	P=0.517	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.597	P=0.011	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.604	P=0.010	P<0.001
Mammary Gland: Carcinoma				
Overall rate	0/52 (0%)	0/50 (0%)	1/51 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	3.8%	8.7%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	0/11 (0%)
First incidence (days)	—[e]	—	743 (T)	520
Life table test	P=0.006	—	P=0.430	P=0.083
Logistic regression test	P=0.028	—	P=0.430	P=0.163
Cochran-Armitage test	P=0.019			
Fisher exact test		—	P=0.495	P=0.114

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Pancreatic Islets: Adenoma				
Overall rate	1/51 (2%)	3/50 (6%)	2/49 (4%)	2/49 (4%)
Adjusted rate	2.1%	10.0%	6.4%	13.2%
Terminal rate	0/37 (0%)	3/30 (10%)	0/26 (0%)	1/11 (9%)
First incidence (days)	569	743 (T)	707	669
Life table test	P=0.164	P=0.252	P=0.456	P=0.274
Logistic regression test	P=0.370	P=0.295	P=0.477	P=0.490
Cochran-Armitage test	P=0.484			
Fisher exact test		P=0.301	P=0.485	P=0.485
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/50 (8%)	8/48 (17%)	2/48 (4%)	5/46 (11%)
Adjusted rate	10.8%	24.0%	8.0%	21.9%
Terminal rate	4/37 (11%)	5/29 (17%)	2/25 (8%)	1/11 (9%)
First incidence (days)	743 (T)	619	743 (T)	537
Life table test	P=0.126	P=0.098	P=0.528N	P=0.093
Logistic regression test	P=0.493	P=0.133	P=0.528N	P=0.421
Cochran-Armitage test	P=0.535N			
Fisher exact test		P=0.159	P=0.359N	P=0.447
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	8/48 (17%)	3/48 (6%)	5/46 (11%)
Adjusted rate	10.8%	24.0%	12.0%	21.9%
Terminal rate	4/37 (11%)	5/29 (17%)	3/25 (12%)	1/11 (9%)
First incidence (days)	743 (T)	619	743 (T)	537
Life table test	P=0.103	P=0.098	P=0.603	P=0.093
Logistic regression test	P=0.452	P=0.133	P=0.603	P=0.421
Cochran-Armitage test	P=0.553N			
Fisher exact test		P=0.159	P=0.523N	P=0.447
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/52 (0%)	1/50 (2%)	4/51 (8%)	11/50 (22%)
Adjusted rate	0.0%	3.1%	11.1%	38.1%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	1/11 (9%)
First incidence (days)	—	696	536	480
Life table test	P<0.001	P=0.466	P=0.053	P<0.001
Logistic regression test	P<0.001	P=0.491	P=0.058	P=0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.490	P=0.057	P<0.001
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/52 (0%)	1/50 (2%)	4/51 (8%)	12/50 (24%)
Adjusted rate	0.0%	3.1%	11.1%	42.8%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	1/11 (9%)
First incidence (days)	—	696	536	480
Life table test	P<0.001	P=0.466	P=0.053	P<0.001
Logistic regression test	P<0.001	P=0.491	P=0.058	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.490	P=0.057	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/52 (0%)	1/50 (2%)	5/51 (10%)	3/50 (6%)
Adjusted rate	0.0%	2.4%	16.6%	24.0%
Terminal rate	0/37 (0%)	0/30 (0%)	3/26 (12%)	2/11 (18%)
First incidence (days)	—	625	639	677
Life table test	P=0.003	P=0.495	P=0.017	P=0.008
Logistic regression test	P=0.022	P=0.504	P=0.029	P=0.028
Cochran-Armitage test	P=0.070			
Fisher exact test		P=0.490	P=0.027	P=0.114
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/51 (6%)	1/50 (2%)	3/51 (6%)	0/50 (0%)
Adjusted rate	8.1%	3.3%	10.6%	0.0%
Terminal rate	3/37 (8%)	1/30 (3%)	2/26 (8%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	709	—
Life table test	P=0.429N	P=0.382N	P=0.509	P=0.396N
Logistic regression test	P=0.355N	P=0.382N	P=0.589	P=0.396N
Cochran-Armitage test	P=0.137N			
Fisher exact test		P=0.316N	P=0.661N	P=0.125N
Uterus: Stromal Polyp				
Overall rate	3/52 (6%)	1/50 (2%)	0/51 (0%)	1/50 (2%)
Adjusted rate	8.1%	3.3%	0.0%	8.3%
Terminal rate	3/37 (8%)	1/30 (3%)	0/26 (0%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	—	733
Life table test	P=0.487N	P=0.382N	P=0.189N	P=0.698
Logistic regression test	P=0.448N	P=0.382N	P=0.189N	P=0.711N
Cochran-Armitage test	P=0.207N			
Fisher exact test		P=0.342N	P=0.125N	P=0.324N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	3/52 (6%)	2/50 (4%)	0/51 (0%)	3/50 (6%)
Adjusted rate	8.1%	6.7%	0.0%	18.3%
Terminal rate	3/37 (8%)	2/30 (7%)	0/26 (0%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	—	615
Life table test	P=0.206	P=0.596N	P=0.189N	P=0.194
Logistic regression test	P=0.361	P=0.596N	P=0.189N	P=0.388
Cochran-Armitage test	P=0.584			
Fisher exact test		P=0.519N	P=0.125N	P=0.642
All Organs: Hemangiosarcoma				
Overall rate	0/52 (0%)	0/50 (0%)	0/51 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	20.9%
Terminal rate	0/37 (0%)	0/30 (0%)	0/26 (0%)	1/11 (9%)
First incidence (days)	—	—	—	672
Life table test	P<0.001	—	—	P=0.013
Logistic regression test	P=0.005	—	—	P=0.055
Cochran-Armitage test	P=0.011			
Fisher exact test		—	—	P=0.114

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/52 (2%)	2/50 (4%)	0/51 (0%)	5/50 (10%)
Adjusted rate	2.7%	5.6%	0.0%	27.0%
Terminal rate	1/37 (3%)	0/30 (0%)	0/26 (0%)	1/11 (9%)
First incidence (days)	743 (T)	635	—	649
Life table test	P=0.003	P=0.453	P=0.570N	P=0.008
Logistic regression test	P=0.024	P=0.484	P=0.570N	P=0.039
Cochran-Armitage test	P=0.041			
Fisher exact test		P=0.485	P=0.505N	P=0.094
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	5/52 (10%)	10/50 (20%)	9/51 (18%)	4/50 (8%)
Adjusted rate	12.5%	25.5%	27.6%	36.4%
Terminal rate	4/37 (11%)	5/30 (17%)	5/26 (19%)	4/11 (36%)
First incidence (days)	285	386	543	743 (T)
Life table test	P=0.193	P=0.089	P=0.092	P=0.165
Logistic regression test	P=0.334N	P=0.121	P=0.183	P=0.607
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.115	P=0.184	P=0.525N
All Organs: Histiocytic Sarcoma				
Overall rate	1/52 (2%)	4/50 (8%)	2/51 (4%)	1/50 (2%)
Adjusted rate	2.7%	11.6%	7.3%	3.3%
Terminal rate	1/37 (3%)	2/30 (7%)	1/26 (4%)	0/11 (0%)
First incidence (days)	743 (T)	579	726	610
Life table test	P=0.440	P=0.140	P=0.387	P=0.579
Logistic regression test	P=0.517N	P=0.165	P=0.442	P=0.739
Cochran-Armitage test	P=0.415N			
Fisher exact test		P=0.169	P=0.493	P=0.743
All Organs: Benign Neoplasms				
Overall rate	29/52 (56%)	29/50 (58%)	29/51 (57%)	34/50 (68%)
Adjusted rate	63.7%	75.9%	75.4%	93.9%
Terminal rate	21/37 (57%)	21/30 (70%)	17/26 (65%)	9/11 (82%)
First incidence (days)	285	619	557	480
Life table test	P<0.001	P=0.246	P=0.146	P<0.001
Logistic regression test	P=0.020	P=0.478	P=0.536	P=0.058
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.489	P=0.535	P=0.143
All Organs: Malignant Neoplasms				
Overall rate	17/52 (33%)	33/50 (66%)	31/51 (61%)	36/50 (72%)
Adjusted rate	40.9%	68.5%	74.0%	91.7%
Terminal rate	13/37 (35%)	15/30 (50%)	16/26 (62%)	8/11 (73%)
First incidence (days)	285	386	397	456
Life table test	P<0.001	P=0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.004	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P=0.004	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/52 (71%)	43/50 (86%)	43/51 (84%)	42/50 (84%)
Adjusted rate	76.8%	89.5%	93.3%	97.6%
Terminal rate	26/37 (70%)	25/30 (83%)	23/26 (88%)	10/11 (91%)
First incidence (days)	285	386	397	456
Life table test	P<0.001	P=0.043	P=0.013	P<0.001
Logistic regression test	P=0.059	P=0.055	P=0.086	P=0.042
Cochran-Armitage test	P=0.114			
Fisher exact test		P=0.056	P=0.085	P=0.094

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pancreatic islets, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Harderian Gland Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carconoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	3/50	0/50	3/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	3/50	0/50	3/50
Ethylene Glycol	2/50	0/50	2/50
Nitrofurantoin	1/50	1/50	2/50
o-Nitroanisole	0/50	1/50	1/50
p-Nitrobenzoic Acid	3/50	0/50	3/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	5/1,470 (3.5%)	8/1,470 (0.5%)	59/1,470 (4.0%)
Standard deviation	3.1%	0.9%	3.1%
Range	0%-10%	0%-2%	0%-10%

[a] Data as of 31 March 1993

TABLE D4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carconoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	1/50	0/50	1/50
C.I. Pigment Red 23	1/50	0/50	1/50
C.I. Pigment Red 3	3/50	1/50	4/50
Ethylene Glycol	0/50	1/50	1/50
Nitrofurantoin	2/50	1/50	3/50
o-Nitroanisole	4/50	2/50	6/50
p-Nitrobenzoic Acid	3/50	0/50	3/50
Polysorbate 80	3/50	0/50	3/50
Rhodamine 6G	3/50	1/50	4/50
Roxarsone	1/50	2/50	3/50
Overall Historical Incidence			
Total	89/1,469 (5.6%)	30/1,469 (2.0%)	110/1,469 (7.5%)
Standard deviation	4.8%	2.2%	5.0%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 31 March 1993

TABLE D4c
Historical Incidence of Subcutaneous Tissue Skin Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Sarcoma	Fibrosarcoma or Sarcoma
Historical Incidence at Southern Research Institute		
Benzyl Acetate	0/50	0/50
C.I. Pigment Red 23	0/50	0/50
C.I. Pigment Red 3	1/50	3/50
Ethylene Glycol	1/50	1/50
Nitrofurantoin	0/50	0/50
o-Nitroanisole	0/50	0/50
p-Nitrobenzoic Acid	1/50	1/50
Polysorbate 80	0/50	4/50
Rhodamine 6G	0/50	0/50
Roxarsone	0/50	0/50
Overall Historical Incidence		
Total	3/1,470 (0.2%)	21/1,470 (1.4%)
Standard deviation	0.6%	2.2%
Range	0%-2%	0%-8%

[a] Data as of 31 March 1993

TABLE D4d
Historical Incidence of Forestomach Squamous Cell Papilloma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Ethylene Glycol	0/50
Nitrofurantoin	1/50
o-Nitroanisole	3/50
p-Nitrobenzoic Acid	1/50
Polysorbate 80	0/50
Rhodamine 6G	1/50
Roxarsone	0/50
Overall Historical Incidence	
Total	31/1,470 (2.1%)
Standard deviation	2.9%
Range	0%-14%

[a] Data as of 31 March 1993

TABLE D4e
Historical Incidence of Mammary Gland Adenoacanthoma and Carcinoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Adenoacanthoma	Carcinoma
Historical Incidence at Southern Research Institute		
Benzyl Acetate	0/50	0/50
C.I. Pigment Red 23	0/50	1/50
C.I. Pigment Red 3	0/50	0/50
Ethylene Glycol	0/50	1/50
Nitrofurantoin	0/50	5/50
o-Nitroanisole	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50
Polysorbate 80	0/50	0/50
Rhodamine 6G	0/50	0/50
Roxarsone	0/50	2/50
Overall Historical Incidence		
Total	0/1,470 (0.0%)	22/1,470 (1.5%)
Standard deviation		2.8%
Range		0%-10%

[a] Data as of 31 March 1993

TABLE D4f
Historical Incidence of Hemangioma and Hemangiosarcoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Heamngiosarcoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	2/50	0/50	2/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	2/50	2/50	3/50
Ethylene Glycol	0/50	0/50	0/50
Nitrofurantoin	1/50	2/50	3/50
o-Nitroanisole	2/50	1/50	3/50
p-Nitrobenzoic Acid	0/50	4/50	4/50
Polysorbate 80	1/50	0/50	1/50
Rhodamine 6G	1/50	2/50	2/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	21/1,470 (1.4%)	42/1,470 (2.9%)	60/1470 (4.1%)
Standard deviation	2.0%	2.5%	2.7%
Range	0%-8%	0%-8%	0%-8%

[a] Data as of 31 March 1993

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	8	10	9	10
Early deaths				
Moribund	9	14	14	29
Natural deaths	6	6	11	10
Survivors				
Terminal sacrifice	37	30	26	11
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Esophagus	(8)	(10)	(9)	(10)
Mucosa, hyperplasia				1 (10%)
Liver	(8)	(10)	(9)	(10)
Basophilic focus		1 (10%)		
Eosinophilic focus		1 (10%)		1 (10%)
Inflammation, subacute	2 (25%)	1 (10%)		1 (10%)
Mesentery		(1)	(1)	(2)
Inflammation, chronic			1 (100%)	
Fat, necrosis		1 (100%)		2 (100%)
Pancreas	(8)	(10)	(9)	(10)
Atrophy			1 (11%)	
Focal cellular change		1 (10%)		
Salivary glands	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid		1 (10%)	1 (11%)	1 (10%)
Stomach, forestomach	(8)	(10)	(9)	(10)
Ulcer			2 (22%)	3 (30%)
Mucosa, hyperplasia	1 (13%)		3 (33%)	3 (30%)
Endocrine System				
Adrenal cortex	(8)	(10)	(9)	(10)
Accessory adrenal cortical nodule				2 (20%)
Islets, pancreatic	(8)	(10)	(9)	(10)
Hyperplasia		1 (10%)		
Parathyroid gland	(8)	(9)	(9)	(9)
Cyst			1 (11%)	
Ectopic tissue	1 (13%)			1 (11%)
Pituitary gland	(8)	(10)	(9)	(10)
Pars distalis, hyperplasia, focal	1 (13%)			
Thyroid gland	(8)	(10)	(9)	(9)
Degeneration, cystic		1 (10%)	1 (11%)	
Follicle, cyst		1 (10%)		
Follicular cell, hyperplasia				1 (11%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(8)	(10)	(9)	(10)
Ectasia	7 (88%)	9 (90%)	8 (89%)	10 (100%)
Inflammation, chronic	1 (13%)			
Pigmentation			2 (22%)	
Ovary	(8)	(10)	(9)	(9)
Angiectasis			1 (11%)	1 (11%)
Cyst	1 (13%)	1 (10%)		1 (11%)
Uterus	(8)	(10)	(9)	(10)
Hydrometra		1 (10%)	1 (11%)	1 (10%)
Hyperplasia, cystic	7 (88%)	10 (100%)	9 (100%)	10 (100%)
Inflammation, suppurative	2 (25%)	1 (10%)	1 (11%)	1 (10%)
Metaplasia, squamous				1 (10%)
Hematopoietic System				
Bone marrow	(8)	(10)	(9)	(10)
Hypercellularity				1 (10%)
Lymph node, mandibular	(8)	(10)	(9)	(10)
Hemorrhage			1 (11%)	
Hyperplasia, lymphoid		1 (10%)		
Lymph node, mesenteric	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid	1 (13%)	1 (10%)		
Spleen	(8)	(10)	(9)	(10)
Hematopoietic cell proliferation			1 (11%)	2 (20%)
Pigmentation, hemosiderin				1 (10%)
Lymphoid follicle, hyperplasia				1 (10%)
Integumentary System				
Skin	(7)	(10)	(9)	(10)
Inflammation, subacute				1 (10%)
Musculoskeletal System				
Bone	(8)	(10)	(9)	(10)
Hyperostosis	1 (13%)			1 (10%)
Respiratory System				
Lung	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid			1 (11%)	
Infiltration cellular, histiocyte	1 (13%)			
Thrombosis			1 (11%)	
Alveolar epithelium, hyperplasia	1 (13%)			
Nose	(8)	(10)	(9)	(10)
Exudate	1 (13%)		1 (11%)	
Special Senses System				
Harderian gland	(4)	(5)	(4)	(7)
Hyperplasia			1 (25%)	1 (14%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(8)	(10)	(9)	(10)
Casts protein	2 (25%)	5 (50%)	3 (33%)	4 (40%)
Cyst	1 (13%)		1 (11%)	1 (10%)
Hyperplasia, lymphoid		2 (20%)	2 (22%)	
Renal tubule, regeneration		1 (10%)		1 (10%)
Transitional epithelium, hyperplasia		1 (10%)		
Urinary bladder	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid		1 (10%)	1 (11%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Nervous System				
2-Year Study				
Alimentary System				
Gallbladder	(49)	(47)	(47)	(45)
Dilatation			2 (4%)	1 (2%)
Intestine large, cecum	(52)	(50)	(49)	(50)
Edema	3 (6%)	1 (2%)	4 (8%)	4 (8%)
Intestine small, duodenum	(51)	(50)	(47)	(49)
Ulcer	1 (2%)			
Intestine small, jejunum	(49)	(49)	(49)	(47)
Peyer's patch, hyperplasia	1 (2%)			
Intestine small, ileum	(51)	(50)	(47)	(47)
Amyloid deposition		1 (2%)		
Liver	(51)	(50)	(50)	(49)
Basophilic focus	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Clear cell focus		1 (2%)		
Cyst			1 (2%)	
Degeneration, fatty	1 (2%)		1 (2%)	3 (6%)
Developmental malformation	1 (2%)			1 (2%)
Eosinophilic focus	4 (8%)	1 (2%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	9 (18%)	6 (12%)	4 (8%)	15 (31%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, subacute	5 (10%)	2 (4%)	2 (4%)	1 (2%)
Mixed cell focus	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Centrilobular, necrosis		1 (2%)	2 (4%)	2 (4%)
Kupffer cell, hyperplasia	6 (12%)	4 (8%)	7 (14%)	12 (24%)
Kupffer cell, pigmentation	2 (4%)		1 (2%)	1 (2%)
Lobules, necrosis	4 (8%)	7 (14%)	6 (12%)	6 (12%)
Mesentery	(4)	(6)	(7)	(6)
Inflammation, chronic			1 (14%)	
Fat, necrosis	4 (100%)	5 (83%)	4 (57%)	5 (83%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(51)	(50)	(49)	(48)
Atrophy	1 (2%)	3 (6%)	2 (4%)	5 (10%)
Cyst	1 (2%)	2 (4%)	3 (6%)	5 (10%)
Focal cellular change				4 (8%)
Hyperplasia, lymphoid		2 (4%)		2 (4%)
Acinar cell, cytoplasmic alteration	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Salivary glands	(52)	(50)	(51)	(50)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	5 (10%)	4 (8%)
Stomach, forestomach	(51)	(50)	(51)	(49)
Diverticulum		1 (2%)	1 (2%)	
Inflammation, suppurative			1 (2%)	1 (2%)
Ulcer	5 (10%)	2 (4%)	5 (10%)	3 (6%)
Mucosa, hyperkeratosis				1 (2%)
Mucosa, hyperplasia	9 (18%)	5 (10%)	13 (25%)	6 (12%)
Stomach, glandular	(51)	(50)	(49)	(49)
Ectopic tissue	1 (2%)			
Edema	1 (2%)		1 (2%)	2 (4%)
Erosion	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Inflammation, subacute	3 (6%)	1 (2%)	1 (2%)	
Mineralization			1 (2%)	1 (2%)
Ulcer				1 (2%)
Mucosa, hyperplasia	1 (2%)	1 (2%)	2 (4%)	
Cardiovascular System				
Blood vessel	(1)			
Inflammation, subacute	1 (100%)			
Heart	(52)	(50)	(51)	(50)
Inflammation, chronic			1 (2%)	1 (2%)
Mineralization			1 (2%)	1 (2%)
Thrombosis		1 (2%)	1 (2%)	1 (2%)
Myocardium, necrosis			1 (2%)	
Endocrine System				
Adrenal cortex	(51)	(50)	(51)	(49)
Accessory adrenal cortical nodule	5 (10%)	6 (12%)	6 (12%)	4 (8%)
Angiectasis		1 (2%)		
Cyst		2 (4%)		
Degeneration, fatty		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal				1 (2%)
Hypertrophy, focal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Capsule, hyperplasia	1 (2%)	1 (2%)		
Adrenal medulla	(51)	(50)	(51)	(49)
Atrophy	1 (2%)			
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Islets, pancreatic	(51)	(50)	(49)	(49)
Hyperplasia	2 (4%)	1 (2%)		3 (6%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Parathyroid gland	(44)	(45)	(49)	(47)
Cyst	2 (5%)	4 (9%)	2 (4%)	
Pituitary gland	(50)	(48)	(48)	(46)
Pars distalis, angiectasis	3 (6%)	2 (4%)	5 (10%)	1 (2%)
Pars distalis, cyst	1 (2%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	8 (16%)	4 (8%)	5 (10%)	8 (17%)
Thyroid gland	(51)	(50)	(51)	(50)
Degeneration, cystic	12 (24%)	6 (12%)	13 (25%)	14 (28%)
Ectopic thymus			1 (2%)	
Follicle, cyst	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Follicular cell, hyperplasia	13 (25%)	15 (30%)	9 (18%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(52)	(48)	(51)	(50)
Ectasia	2 (4%)		2 (4%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)	
Ovary	(51)	(49)	(51)	(48)
Angiectasis	9 (18%)	5 (10%)	17 (33%)	11 (23%)
Cyst	10 (20%)	12 (24%)	11 (22%)	16 (33%)
Inflammation, suppurative	8 (16%)	2 (4%)	4 (8%)	6 (13%)
Uterus	(52)	(50)	(51)	(50)
Angiectasis	2 (4%)	6 (12%)	16 (31%)	17 (34%)
Hydrometra	10 (19%)	5 (10%)	7 (14%)	4 (8%)
Hyperplasia, cystic	46 (88%)	41 (82%)	43 (84%)	45 (90%)
Inflammation, granulomatous			1 (2%)	1 (2%)
Inflammation, suppurative	9 (17%)	2 (4%)	5 (10%)	2 (4%)
Metaplasia, squamous	4 (8%)	3 (6%)		
Hematopoietic System				
Bone marrow	(52)	(50)	(51)	(50)
Hypercellularity	13 (25%)	15 (30%)	15 (29%)	25 (50%)
Myelofibrosis	7 (13%)	5 (10%)	6 (12%)	7 (14%)
Necrosis	1 (2%)			
Lymph node	(9)	(12)	(6)	(9)
Bronchial, hyperplasia, lymphoid	1 (11%)			
Iliac, hematopoietic cell proliferation	1 (11%)		1 (17%)	1 (11%)
Iliac, hyperplasia, lymphoid	6 (67%)	1 (8%)		3 (33%)
Inguinal, hyperplasia, lymphoid		1 (8%)		
Mediastinal, hyperplasia, lymphoid	2 (22%)		1 (17%)	3 (33%)
Mediastinal, inflammation, suppurative				1 (11%)
Pancreatic, hematopoietic cell proliferation				1 (11%)
Pancreatic, hyperplasia, lymphoid				1 (11%)
Pancreatic, necrosis		1 (8%)		
Renal, hyperplasia, lymphoid	6 (67%)	2 (17%)		5 (56%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(46)	(50)	(46)
Atrophy	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	1 (2%)		2 (4%)
Hemorrhage				2 (4%)
Hyperplasia, lymphoid	5 (10%)	6 (13%)	8 (16%)	11 (24%)
Pigmentation	6 (13%)	5 (11%)		7 (15%)
Lymph node, mesenteric	(49)	(48)	(46)	(48)
Angiectasis	1 (2%)	1 (2%)	2 (4%)	
Atrophy	1 (2%)			
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hemorrhage	4 (8%)	4 (8%)	1 (2%)	4 (8%)
Hyperplasia, lymphoid	5 (10%)	3 (6%)	4 (9%)	9 (19%)
Pigmentation				1 (2%)
Spleen	(51)	(50)	(50)	(50)
Hematopoietic cell proliferation	20 (39%)	25 (50%)	25 (50%)	39 (78%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)	
Pigmentation, hemosiderin	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Lymphoid follicle, atrophy	1 (2%)			
Lymphoid follicle, hyperplasia	8 (16%)	3 (6%)	6 (12%)	4 (8%)
Red pulp, atrophy	1 (2%)			
Thymus	(46)	(47)	(46)	(42)
Atrophy	2 (4%)	3 (6%)	4 (9%)	4 (10%)
Ectopic parathyroid gland	1 (2%)			
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Integumentary System				
Mammary gland	(52)	(50)	(50)	(49)
Hyperplasia, cystic	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, lobular	1 (2%)	2 (4%)	1 (2%)	
Skin	(52)	(50)	(51)	(50)
Acanthosis		1 (2%)		
Edema			1 (2%)	1 (2%)
Inflammation, subacute		1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(52)	(50)	(51)	(50)
Hyperostosis	1 (2%)		3 (6%)	2 (4%)
Nervous System				
Brain	(52)	(50)	(51)	(50)
Compression		4 (8%)	2 (4%)	
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, chronic			2 (4%)	
Necrosis			1 (2%)	
Peripheral nerve	(1)	(1)	(1)	(1)
Atrophy	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(52)	(50)	(51)	(50)
Congestion		1 (2%)	1 (2%)	
Foreign body		1 (2%)		1 (2%)
Hemorrhage	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	3 (6%)	5 (10%)	6 (12%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	5 (10%)	5 (10%)	5 (10%)
Inflammation, subacute	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Mineralization			1 (2%)	
Thrombosis	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	3 (6%)	8 (16%)	15 (30%)
Nose	(52)	(50)	(51)	(50)
Exudate	2 (4%)		1 (2%)	
Special Senses System				
Eye		(2)	(3)	(7)
Cataract		2 (100%)	1 (33%)	2 (29%)
Inflammation, chronic		1 (50%)		5 (71%)
Phthisis bulbi			2 (67%)	1 (14%)
Harderian gland	(18)	(27)	(27)	(33)
Hyperplasia	1 (6%)	1 (4%)	2 (7%)	
Urinary System				
Kidney	(51)	(50)	(51)	(49)
Casts protein	17 (33%)	17 (34%)	13 (25%)	4 (8%)
Cyst	1 (2%)		1 (2%)	
Glomerulosclerosis	1 (2%)	1 (2%)		
Hydronephrosis				1 (2%)
Hyperplasia, lymphoid	9 (18%)	9 (18%)	5 (10%)	4 (8%)
Metaplasia, osseous	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		2 (4%)	1 (2%)
Renal tubule, atrophy	1 (2%)			
Renal tubule, cytoplasmic alteration	1 (2%)	1 (2%)	2 (4%)	
Renal tubule, dilatation	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Renal tubule, necrosis			2 (4%)	1 (2%)
Renal tubule, pigmentation	1 (2%)		1 (2%)	1 (2%)
Renal tubule, regeneration	7 (14%)	10 (20%)	11 (22%)	6 (12%)
Urinary bladder	(51)	(50)	(50)	(50)
Edema	1 (2%)		2 (4%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, subacute			2 (4%)	1 (2%)
Mucosa, hyperplasia	1 (2%)		2 (4%)	1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986) and Zeiger *et al.* (1992). 2,2-Bis(bromomethyl)-1,3-propanediol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of 2,2-bis(bromomethyl)-1,3-propanediol. The high dose was limited by toxicity in the second study. Because toxicity was not a limiting factor in the first study, 10,000 μg/plate was selected as the high dose. All positive assays were repeated under the conditions which elicited the positive response.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 2,2-Bis(bromomethyl)-1,3-propanediol was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of 2,2-bis(bromomethyl)-1,3-propanediol; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26.3 hours with 2,2-bis(bromomethyl)-1,3-propanediol in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26.3 hours, the medium containing 2,2-bis(bromomethyl)-1,3-propanediol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 2,2-bis(bromomethyl)-1,3-propanediol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 2,2-bis(bromomethyl)-1,3-propanediol, and incubation proceeded for an additional 25.5 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Generally, fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in the test without S9, incubation time was

lengthened at the 167 and 500 μg/kg dose levels to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with 2,2-bis(bromomethyl)-1,3-propanediol for 18.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 2,2-bis(bromomethyl)-1,3-propanediol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test. Because cell cycle delay was anticipated in the test conducted without S9, the incubation period was extended approximately 10 to 12 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Generally, 100 first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose led to an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Mouse Bone Marrow Micronucleus Test Protocols

Two bone marrow studies were performed. The first employed a 3-dose gavage protocol, with 2,2-bis(bromomethyl)-1,3-propanediol administered at 24-hour intervals followed by bone marrow sampling 24 hours after the third dosing. The second study used a single intraperitoneal injection followed by bone marrow sampling 48 hours after dosing. In the first study, male $B6C3F_1$ mice were administered 2,2-bis(bromomethyl)-1,3-propanediol in corn oil by gavage three times at 24-hour intervals. Solvent control animals were administered corn oil alone, and the positive control mice received injections of 12.5 mg dimethylbenzanthracene per kg body weight. In the second study, 2,2-bis(bromomethyl)-1,3-propanediol was administered to male and female $B6C3F_1$ mice by a single intraperitoneal injection. The solvent control mice were again administered corn oil and the positive control mice were administered urethane (200 mg/kg). In both studies, smears of the bone marrow cells obtained from the femurs were prepared, air-dried, fixed, and stained. In the gavage study, 2,000 polychromatic erythrocytes (PCEs)

were scored for frequency of micronucleated cells in each of 5 animals per dose group. In the injection study, 3 or 4 animals were available for micronucleus analysis in each dose group, and 1,000 PCEs were scored per animal. The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. For the three-treatment gavage study, the frequency of micronucleated cells among PCEs was analyzed by a statistical software package (ILS, 1990) which employed a one-tailed trend test across dose groups and a *t*-test for pairwise comparisons of each dose group to the concurrent control. Data from the single injection micronucleus test were analyzed by the Cochran-Armitage trend test and pairwise comparisons of dose groups to the corresponding negative controls were made using a *t*-test.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were sent to the USDA Western Regional Research Center in Albany, CA, where they were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630 or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in as many as 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using a Student's *t*-test.

RESULTS

2,2-Bis(bromomethyl)-1,3-propanediol was shown to be mutagenic *in vitro* and *in vivo*, but the conditions required to observe the positive responses were highly specific, and 2,2-bis(bromomethyl)-1,3-propanediol was not active in all assays. In the two *Salmonella* assays reported here (Table E1), 2,2-bis(bromomethyl)-1,3-propanediol gave a positive response only in the second assay (Zeiger *et al.*, 1992), which used a different concentration of S9 than the first assay (Mortelmans *et al.*, 1986). Metabolic activation, specifically in the form of 30% Aroclor 1254-induced male Syrian hamster liver S9, was required to obtain the mutagenic response; 10% hamster S9 was ineffective, as was 10% or 30% S9 derived from livers of pretreated rats. No other *Salmonella* strain/activation combination was responsive to the effects of 2,2-bis(bromomethyl)-1,3-propanediol.

In cytogenetic tests with CHO cells (Galloway *et al.*, 1987), 2,2-bis(bromomethyl)-1,3-propanediol did not induce SCEs, with or without S9 (Table E2), but a dose-related increase in Abs was observed in CHO cells treated in the presence of induced rat liver S9 (Table E3). Both tests were conducted up to doses which induced marked cytotoxicity; cell confluence in the SCE test was reduced 75% at the top dose tested with S9 (1,200 μg/mL). A majority of the breaks which were observed in the aberration assay were located in the heterochromatic region of the long arm of the X chromosome. The reason for this preferential breakage site is not known. Also, the type of damage pattern seen with 2,2-bis(bromomethyl)-

1,3-propanediol (induction of chromosomal aberrations but not sister chromatid exchanges) is unusual. Most chemicals which induce Abs also induce SCEs (Galloway *et al.*, 1987).

2,2-Bis(bromomethyl)-1,3-propanediol was also shown to be genotoxic *in vivo*. Significant increases in micronucleated normochromatic erythrocytes were observed in peripheral blood samples obtained from male and female mice exposed for 13 weeks to 2,2-bis(bromomethyl)-1,3-propanediol in feed (Table E6). These increases were observed in the two highest dose groups of male mice (5,000 and 10,000 ppm) and the three highest dose groups of female mice (2,500 to 10,000 ppm).

In the first of two mouse bone marrow micronucleus tests performed to confirm the positive results seen in the 13-week feed study, inconsistent results were obtained between two trials which used the same dose range of 100 to 400 mg/kg 2,2-bis(bromomethyl)-1,3-propanediol, administered by gavage three times at 24-hour intervals (Table E4). Results of the first trial were negative; however, in the second trial, 2,2-bis(bromomethyl)-1,3-propanediol produced a clear, dose-related increase in micronucleated PCEs. Because the positive response was not reproduced, the results were concluded to be equivocal.

In an attempt to clarify the results obtained in the first bone marrow micronucleus test, a second investigation was performed using both male and female mice. 2,2-Bis(bromomethyl)-1,3-propanediol was administered as a single intraperitoneal injection (150 to 600 mg/kg) and bone marrow samples were taken 48 hours after dosing. The results of this experiment, shown in Table E5, provide evidence of the ability of 2,2-bis(bromomethyl)-1,3-propanediol to induce micronuclei in bone marrow cells of female mice. Although male mice in all three dose groups showed a two-fold increase in the frequency of micronucleated PCEs, the trend test was not significant due to the similarity in the responses, and pairwise analyses were also insignificant. The response in female mice was somewhat stronger (2.5-fold increase over background, at the highest dose) and was directly related to increasing doses of 2,2-bis(bromomethyl)-1,3-propanediol. These results were consistent with the stronger response observed in female mice in the 13-week feed study (Table E4).

In conclusion, 2,2-bis(bromomethyl)-1,3-propanediol was genotoxic *in vitro* and *in vivo*, inducing gene mutations in *Salmonella* strain TA100, chromosomal aberrations in Chinese hamster ovary cells, and micronuclei in erythrocytes of male and female mice. The *in vitro* responses required S9.

TABLE E1
Mutagenicity of 2,2-Bis(bromomethyl)-1,3-propanediol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] −S9 Trial 1	−S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Case Western Reserve University							
TA100	0	69 ± 3.8	83 ± 3.5	77 ± 4.2	94 ± 9.0	81 ± 3.2	76 ± 4.6
	10		64 ± 6.0				
	33	76 ± 1.9	59 ± 6.0				
	100	64 ± 5.3	56 ± 3.5	88 ± 6.2	105 ± 11.3	93 ± 7.3	85 ± 4.8
	333	55 ± 5.0	61 ± 4.0	105 ± 7.5	93 ± 4.0	85 ± 7.3	76 ± 4.8
	1,000	toxic	56 ± 2.5	112 ± 7.2	107 ± 9.5	93 ± 1.2	79 ± 6.0
	3,333	toxic		126 ± 0.0	106 ± 8.5	82 ± 6.9	85 ± 7.0
	10,000			toxic	110 ± 10.0	toxic	71 ± 8.4
Trial summary		Negative	Negative	Weakly Positive	Negative	Negative	Negative
Positive control[c]		625 ± 45.2	429 ± 44.2	1,468 ± 2.9	1,171 ± 157.7	1,362 ± 92.4	1,044 ± 44.5
TA1535	0	6 ± 0.9	7 ± 0.7	6 ± 0.6	10 ± 0.9	8 ± 0.3	6 ± 2.0
	10						
	33	4 ± 0.9	6 ± 0.6				
	100	5 ± 1.9	9 ± 1.5	10 ± 1.7	10 ± 1.3	10 ± 2.1	10 ± 2.0
	333	2 ± 1.0	6 ± 0.6	17 ± 2.4	14 ± 1.9	11 ± 2.2	10 ± 1.2
	1,000	3 ± 1.2	10 ± 1.8	14 ± 3.2	10 ± 4.5	10 ± 0.3	10 ± 0.3
	3,333	2 ± 0.7	toxic	16 ± 3.0	16 ± 1.8	12 ± 1.7	10 ± 0.9
	10,000			12 ± 1.2	14 ± 1.9	10 ± 1.8	11 ± 0.7
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		471 ± 110.0	488 ± 98.5	128 ± 3.9	113 ± 15.5	280 ± 31.9	71 ± 11.6
TA1537	0	2 ± 0.9	6 ± 0.6	6 ± 1.9	10 ± 1.5	7 ± 0.9	10 ± 1.5
	33	1 ± 0.3	4 ± 1.2				
	100	1 ± 0.6	8 ± 0.9	5 ± 0.9	7 ± 1.2	5 ± 1.5	6 ± 1.2
	333	0 ± 0.3	7 ± 1.8	3 ± 0.3	7 ± 1.0	6 ± 2.1	10 ± 1.5
	1,000	0 ± 0.0	3 ± 2.0	6 ± 1.5	10 ± 2.1	2 ± 0.9	9 ± 0.3
	3,333	1 ± 0.3	3 ± 3.0	2 ± 1.0	9 ± 1.2	2 ± 0.9	7 ± 0.6
	10,000			2 ± 0.9	toxic	2 ± 0.6	7 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		432 ± 12.9	55 ± 6.8	74 ± 3.5	52 ± 7.0	58 ± 3.0	71 ± 15.8
TA98	0	21 ± 2.2	18 ± 4.0	11 ± 0.9	21 ± 3.2	10 ± 0.6	23 ± 1.7
	10		11 ± 1.5				
	33	9 ± 1.5	12 ± 1.2				
	100	12 ± 2.4	11 ± 1.2	15 ± 1.8	14 ± 4.4	12 ± 1.2	20 ± 0.3
	333	7 ± 1.3	12 ± 1.5	13 ± 1.8	19 ± 4.6	12 ± 1.0	20 ± 1.2
	1,000	toxic	8 ± 0.3	10 ± 2.1	22 ± 1.2	13 ± 3.4	19 ± 2.3
	3,333	toxic		14 ± 0.6	23 ± 1.9	13 ± 1.2	20 ± 3.8
	10,000			3 ± 0.9	19 ± 3.5	8 ± 1.2	21 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		129 ± 18.0	462 ± 34.7	1,076 ± 45.0	854 ± 74.9	481 ± 83.0	568 ± 8.4

TABLE E1
Mutagenicity of 2,2-Bis(bromomethyl)-1,3-propanediol in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate −S9 Trial 1	−S9 Trial 2	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% rat S9
Study performed at SRI, Inc.						
TA100	0	159 ± 3.5	161 ± 11.1	151 ± 4.7	160 ± 10.2	170 ± 9.0
	10		149 ± 11.8			
	33		164 ± 13.5			
	100	152 ± 7.0	150 ± 10.4	156 ± 8.1	172 ± 11.5	154 ± 10.1
	333	161 ± 12.7	154 ± 5.4	233 ± 15.6	225 ± 17.5	154 ± 3.5
	1,000	154 ± 5.8	188 ± 4.2	335 ± 11.9	364 ± 21.4	157 ± 5.8
	1,666				414 ± 32.8	
	3,333	0 ± 0.0[d]		533 ± 14.9	502 ± 32.4	171 ± 5.5
	6,666	toxic		477 ± 39.8		173 ± 8.1
Trial summary		Negative	Negative	Positive	Positive	Negative
Positive control		503 ± 5.2	1,132 ± 62.5	812 ± 50.9	845 ± 18.8	529 ± 7.9

Strain	Dose (μg/plate)	Revertants/plate −S9 Trial 1	−S9 Trial 2	+30% S9 hamster	+30% S9 rat
TA98	0	28 ± 2.2	32 ± 6.1	35 ± 2.7	43 ± 3.5
	10		32 ± 4.7		
	33		41 ± 5.5		
	100	30 ± 3.5	32 ± 0.3	36 ± 3.5	46 ± 4.5
	333	35 ± 2.9	29 ± 0.6	34 ± 2.9	44 ± 6.1
	1,000	27 ± 3.3	44 ± 4.7	30 ± 1.8	50 ± 5.8
	3,333	23 ± 3.4[d]		39 ± 3.8	31 ± 3.8
	6,666	toxic		29 ± 3.5	40 ± 1.5
Trial summary		Negative	Negative	Negative	Negative
Positive control		677 ± 20.6	464 ± 26.2	770 ± 11.3	168 ± 3.5

[a] The detailed protocol and these data for the study performed at Case Western Reserve University are presented in Mortelmans *et al.* (1986); protocol and data for the study performed at SRI, Inc. are presented in Zeiger *et al.* (1992). 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

[d] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 2,2-Bis(bromomethyl)-1,3-propanediol[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
−S9								
Summary: Negative								
Dimethylsulfoxide		50	1,038	496	0.47	9.9	26.3	
Mitomycin-C	0.005	25	519	692	1.33	27.7	26.3	179.03
2,2-Bis(bromomethyl)-1,3-propanediol	16.7	50	1,041	485	0.46	9.7	26.3	−2.50
	50	50	1,042	498	0.47	10.0	26.3	0.02
	167	50	1,050	545	0.51	10.9	33.5[c]	8.62
	500	0					33.5[c]	
					P=0.077[d]			
+S9								
Summary: Equivocal								
Dimethylsulfoxide		50	1,050	496	0.47	9.9	25.5	
Cyclophosphamide	1.5	25	523	840	1.60	33.6	25.5	240.00
2,2-Bis(bromomethyl)-1,3-propanediol	800	50	1,048	556	0.53	11.1	25.5	12.31
	1,000	50	1,047	590	0.56	11.8	25.5	19.29
	1,200[e]	50	1,046	574	0.54	11.5	25.5	16.17
					P=0.004			

[a] Study performed at Litton Bionetics, Inc. A detailed description of the protocol and these data are presented in Galloway *et al.* (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells.
[c] Due to chemical-induced cell cycle delay, incubation time was extended to provide sufficient cells for scoring.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[e] Marked toxicity noted at this dose level

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2,2-Bis(bromomethyl)-1,3-propanediol[a]

−S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 20.5 hours[b]					Harvest time: 10.5 hours				
Summary: Negative					Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	2	0.02	2.0		100	5	0.05	5.0
Mitomycin-C					Cyclophosphamide				
0.062	50	10	0.20	16.0	50	50	19	0.38	28.0
2,2-Bis(bromomethyl)-1,3-propanediol					2,2-Bis(bromomethyl)-1,3-propanediol				
400	100	1	0.01	1.0	600	100	8	0.08	4.0
500	100	2	0.02	2.0	800	100	24	0.24	22.0*
600	100	0	0.00	0.0	1,000	100	17	0.17	16.0*
700	0				1,200	0			
				P=0.833[c]					P≤0.001

* Positive ($P<0.05$)

[a] Study performed at Litton Bionetics, Inc. The detailed protocol and these data are presented in Galloway *et al.* (1987). Abs = aberrations.

[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.

[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE E4
Frequency of Micronuclei in Bone Marrow Cells of Male Mice Treated with 2,2-Bis(bromomethyl)-1,3-propanediol by Gavage[a]

Dose (mg/kg)[b]	Micronucleated Cells/1,000 PCEs[c]
Trial 1 - Negative	
Dimethylbenzanthracene[d]	
12.5	4.6 ± 1.1
2,2-Bis(bromomethyl)-1,3-propanediol	
0	1.4 ± 0.6
100	0.7 ± 0.4
200	2.5 ± 0.5
300	2.0 ± 0.7
400[e]	1.2 ± 1.2
	P=0.220[f]
Trial 2 - Positive	
Dimethylbenzanthracene	
12.5	7.8 ± 1.3
2,2-Bis(bromomethyl)-1,3-propanediol	
0	1.5 ± 0.5
100	2.3 ± 0.3
200	2.6 ± 0.7
400	4.8 ± 1.2*
	P=0.000

* Significantly different (P<0.008) from control
[a] Study performed at Environmental Health Research and Testing, Inc. Two thousand PCEs scored per animal.
[b] 0 mg/kg dose is corn oil control.
[c] Data presented as mean ± standard error; PCE = polychromatic erythrocyte
[d] Positive control
[e] Only 2 mice survived in this dose group.
[f] Trend test

TABLE E5
Frequency of Micronuclei in Bone Marrow Cells of Mice Treated with 2,2-Bis(bromomethyl)-1,3-propanediol by Intraperitoneal Injection[a]

Dose (mg/kg)[b]	Number of Mice	Micronucleated Cells/1,000 PCEs[c]
Male		
Urethane[d]		
200	3	16.4 ± 2.2
2,2-Bis(bromomethyl)-1,3-propanediol		
0	4	1.5 ± 0.3
150	4	3.2 ± 0.8*
300	4	3.0 ± 0.7*
600	3	3.0 ± 1.0*
		P=0.150[e]
Female		
Urethane		
200	4	12.1 ± 0.9
2,2-Bis(bromomethyl)-1,3-propanediol		
0	4	2.0 ± 0.4
150	4	2.7 ± 1.1
300	3	3.6 ± 0.9*
600	4	5.2 ± 0.5*
		P=0.003

* Significantly different ($P<0.008$) from control
[a] One thousand PCEs scored per animal. 2,2-Bis(bromomethyl)-1,3-propanediol was administered by intraperitoneal injection, and bone marrow was sampled 48 hours later.
[b] 0 mg/kg dose is corn oil control.
[c] Data presented as mean ± standard error; PCE = polychromatic erythrocyte
[d] Positive control
[e] Trend test

TABLE E6
Frequency of Micronucleated Normochromatic Erythrocytes in Mouse Peripheral Blood Following Treatment with 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 13 Weeks[a]

Dose (ppm)	Micronucleated NCEs/1,000 Cells[b]	Number of Mice
Male		
0	2.36 ± 0.17	10
625	2.28 ± 0.29	8
1,250	2.55 ± 0.18	10
2,500	2.98 ± 0.21	10
5,000	3.80 ± 0.19[c]	10
10,000	9.30 ± 1.26[c]	7
	P<0.001[d]	
Female		
0	1.46 ± 0.26	9
625	1.86 ± 0.30	9
1,250	1.86 ± 0.22	9
2,500	2.72 ± 0.32[c]	9
5,000	4.26 ± 0.47[c]	9
10,000	11.81 ± 0.54[c]	9
	P<0.001	

[a] Ten thousand NCEs scored per animal. The detailed protocol and these data are presented in MacGregor *et al.* (1990). 0 ppm is the control.
[b] Data presented as mean ± standard error; NCE = normochromatic erythrocyte
[c] Significant response by pairwise comparison to control
[d] Trend test

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Core Study						
Male						
n	10	10	10	10	10	9
Necropsy body wt	334 ± 6	336 ± 5	317 ± 4	308 ± 10*	299 ± 8**	255 ± 7**
Brain						
Absolute	2.037 ± 0.019	2.010 ± 0.023	2.028 ± 0.022	2.018 ± 0.023	1.981 ± 0.012	1.948 ± 0.016**
Relative	6.13 ± 0.12	6.00 ± 0.11	6.41 ± 0.06	6.60 ± 0.16*	6.66 ± 0.15**	7.69 ± 0.16**
Heart						
Absolute	1.214 ± 0.035	1.225 ± 0.043	1.196 ± 0.025	1.202 ± 0.037	1.182 ± 0.053	1.152 ± 0.048
Relative	3.65 ± 0.12	3.65 ± 0.13	3.78 ± 0.06	3.93 ± 0.17	3.95 ± 0.13	4.50 ± 0.21**
R. Kidney						
Absolute	1.224 ± 0.027	1.251 ± 0.029	1.234 ± 0.014	1.227 ± 0.038	1.240 ± 0.024	1.173 ± 0.028
Relative	3.68 ± 0.09	3.73 ± 0.06	3.90 ± 0.06	3.99 ± 0.09*	4.16 ± 0.11**	4.62 ± 0.12**
Liver						
Absolute	12.534 ± 0.167	12.106 ± 0.375	12.071 ± 0.258	12.206 ± 0.524	13.200 ± 0.231	12.322 ± 0.300
Relative	37.64 ± 0.48	36.03 ± 0.69	38.18 ± 0.90	39.61 ± 0.98	44.32 ± 0.99**	48.49 ± 1.08**
Lungs						
Absolute	1.660 ± 0.082	1.856 ± 0.059	1.663 ± 0.088	1.523 ± 0.038	1.630 ± 0.042	1.376 ± 0.048**
Relative	4.97 ± 0.21	5.55 ± 0.22	5.25 ± 0.26	4.98 ± 0.16	5.49 ± 0.22	5.45 ± 0.26
Spleen						
Absolute	0.736 ± 0.015	0.745 ± 0.015	0.701 ± 0.014	0.689 ± 0.019	0.718 ± 0.013	0.620 ± 0.012**
Relative	2.21 ± 0.04	2.22 ± 0.04	2.21 ± 0.03	2.25 ± 0.05	2.41 ± 0.06**	2.43 ± 0.06**
R. Testis						
Absolute	1.492 ± 0.027	1.458 ± 0.038[b]	1.503 ± 0.019[b]	1.443 ± 0.035	1.411 ± 0.038	1.360 ± 0.036**
Relative	4.49 ± 0.12	4.36 ± 0.09[b]	4.76 ± 0.07[b]	4.71 ± 0.14	4.74 ± 0.13	5.31 ± 0.15**
Thymus						
Absolute	0.319 ± 0.010	0.335 ± 0.013	0.317 ± 0.024	0.286 ± 0.014	0.270 ± 0.019	0.251 ± 0.019**
Relative	0.96 ± 0.02	1.00 ± 0.04	1.00 ± 0.07	0.94 ± 0.05	0.90 ± 0.06	0.96 ± 0.08
Female						
n	10	10	10	10	10	10
Necropsy body wt	200 ± 6	192 ± 3	189 ± 2	184 ± 3**	174 ± 6**	163 ± 2**
Brain						
Absolute	1.912 ± 0.022	1.899 ± 0.013	1.838 ± 0.018*	1.856 ± 0.018	1.888 ± 0.017	1.861 ± 0.015
Relative	9.65 ± 0.29	9.90 ± 0.12	9.73 ± 0.10	10.09 ± 0.12	11.01 ± 0.46**	11.43 ± 0.19**
Heart						
Absolute	0.836 ± 0.018	0.796 ± 0.029	0.781 ± 0.018	0.788 ± 0.023	0.793 ± 0.023	0.748 ± 0.029
Relative	4.20 ± 0.10	4.14 ± 0.14	4.13 ± 0.10	4.29 ± 0.14	4.62 ± 0.22	4.59 ± 0.17
R. Kidney						
Absolute	0.772 ± 0.022	0.757 ± 0.017	0.728 ± 0.019	0.749 ± 0.022	0.728 ± 0.014	0.710 ± 0.017
Relative	3.88 ± 0.10	3.94 ± 0.07	3.85 ± 0.09	4.06 ± 0.09	4.25 ± 0.20*	4.35 ± 0.07**
Liver						
Absolute	6.891 ± 0.209	6.567 ± 0.147	6.470 ± 0.204	6.679 ± 0.135	6.253 ± 0.120**	6.317 ± 0.044**
Relative	34.58 ± 0.80	34.21 ± 0.66	34.20 ± 0.92	36.25 ± 0.40	36.39 ± 1.41	38.81 ± 0.66**
Lungs						
Absolute	1.142 ± 0.039	1.159 ± 0.050	1.027 ± 0.018	1.213 ± 0.037	1.060 ± 0.022	1.075 ± 0.037
Relative	5.75 ± 0.21	6.03 ± 0.22	5.44 ± 0.10	6.60 ± 0.23	6.18 ± 0.29	6.60 ± 0.24*
Spleen						
Absolute	0.519 ± 0.013	0.516 ± 0.013	0.520 ± 0.006	0.524 ± 0.010	0.517 ± 0.007	0.509 ± 0.007
Relative	2.62 ± 0.10	2.69 ± 0.06	2.75 ± 0.03	2.85 ± 0.06*	3.01 ± 0.12**	3.13 ± 0.07**
Thymus						
Absolute	0.279 ± 0.009	0.275 ± 0.018	0.267 ± 0.016	0.259 ± 0.019	0.248 ± 0.012	0.239 ± 0.009
Relative	1.40 ± 0.06	1.43 ± 0.09	1.41 ± 0.09	1.40 ± 0.08	1.45 ± 0.10	1.47 ± 0.06

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study						
Male						
n	9	8	9	7	10	10
Necropsy body wt	323 ± 5	327 ± 5	320 ± 3	326 ± 4	302 ± 8**	249 ± 3**
Brain						
Absolute	1.976 ± 0.023	1.994 ± 0.021	1.978 ± 0.036	2.011 ± 0.037	1.976 ± 0.024	1.941 ± 0.024
Relative	6.13 ± 0.05	6.11 ± 0.13	6.18 ± 0.11	6.17 ± 0.09	6.59 ± 0.22*	7.80 ± 0.12**
Heart						
Absolute	1.113 ± 0.034	1.201 ± 0.059	1.171 ± 0.033	1.139 ± 0.039	1.068 ± 0.029	0.985 ± 0.024*
Relative	3.45 ± 0.09	3.69 ± 0.22	3.66 ± 0.09	3.49 ± 0.09	3.56 ± 0.13	3.96 ± 0.11*
R. Kidney						
Absolute	1.353 ± 0.114	1.359 ± 0.032	1.360 ± 0.108	1.355 ± 0.046	1.291 ± 0.034	1.247 ± 0.017
Relative	4.20 ± 0.36	4.16 ± 0.08	4.26 ± 0.36	4.15 ± 0.10	4.29 ± 0.13	5.01 ± 0.07*
Liver						
Absolute	13.691 ± 0.625	15.016 ± 0.646	14.283 ± 0.667	15.543 ± 0.634	15.860 ± 0.638	13.315 ± 0.459
Relative	42.30 ± 1.37	45.85 ± 1.60	44.58 ± 1.98	47.68 ± 1.70	52.81 ± 2.39**	53.46 ± 1.69**
Lung						
Absolute	2.201 ± 0.300	1.959 ± 0.169[c]	1.681 ± 0.083*	1.755 ± 0.070*	1.581 ± 0.060**	1.442 ± 0.034**
Relative	6.83 ± 0.94	6.00 ± 0.50[c]	5.25 ± 0.26	5.39 ± 0.21	5.26 ± 0.20	5.79 ± 0.08
Spleen						
Absolute	0.668 ± 0.024	0.693 ± 0.017	0.699 ± 0.011	0.738 ± 0.016*	0.687 ± 0.014	0.590 ± 0.014**
Relative	2.07 ± 0.06	2.12 ± 0.04	2.18 ± 0.03	2.27 ± 0.05*	2.29 ± 0.09**	2.37 ± 0.03**
R. Testis						
Absolute	1.471 ± 0.020	1.449 ± 0.018	1.484 ± 0.017	1.470 ± 0.026	1.429 ± 0.018	1.405 ± 0.035
Relative	4.57 ± 0.09	4.44 ± 0.07	4.64 ± 0.06	4.51 ± 0.07	4.76 ± 0.12	5.64 ± 0.14**
Thymus						
Absolute	0.304 ± 0.023	0.328 ± 0.025	0.291 ± 0.032	0.280 ± 0.017	0.313 ± 0.023	0.261 ± 0.017
Relative	0.95 ± 0.07	1.00 ± 0.08	0.91 ± 0.10	0.86 ± 0.05	1.04 ± 0.07	1.05 ± 0.06
Female						
n	9	10	9	10	9	10
Necropsy body wt	205 ± 2	204 ± 3	199 ± 2	194 ± 3**	193 ± 3**	170 ± 2**
Brain						
Absolute	1.852 ± 0.023	1.858 ± 0.020	1.876 ± 0.010	1.845 ± 0.024	1.876 ± 0.028	1.808 ± 0.025
Relative	9.05 ± 0.08	9.14 ± 0.14	9.44 ± 0.09	9.50 ± 0.11*	9.73 ± 0.13**	10.64 ± 0.20**
Heart						
Absolute	0.788 ± 0.022	0.745 ± 0.021	0.786 ± 0.024	0.783 ± 0.029	0.766 ± 0.030	0.692 ± 0.021*
Relative	3.85 ± 0.10	3.67 ± 0.11	3.95 ± 0.13	4.04 ± 0.15	3.97 ± 0.14	4.07 ± 0.14
R. Kidney						
Absolute	0.874 ± 0.019	0.850 ± 0.013	0.867 ± 0.016	0.813 ± 0.013*	0.850 ± 0.015	0.816 ± 0.014*
Relative	4.27 ± 0.08	4.18 ± 0.08	4.36 ± 0.06	4.18 ± 0.05	4.41 ± 0.04	4.79 ± 0.06**
Liver						
Absolute	8.255 ± 0.328	8.357 ± 0.329	8.053 ± 0.223	7.813 ± 0.160	8.054 ± 0.225	7.506 ± 0.201
Relative	40.31 ± 1.40	41.09 ± 1.61	40.49 ± 1.14	40.29 ± 0.99	41.79 ± 1.24	44.18 ± 1.39
Lung						
Absolute	1.348 ± 0.023	1.335 ± 0.043	1.367 ± 0.055	1.250 ± 0.068	1.165 ± 0.035*	1.211 ± 0.036*
Relative	6.59 ± 0.14	6.55 ± 0.14	6.87 ± 0.27	6.44 ± 0.37	6.04 ± 0.15	7.12 ± 0.19
Spleen						
Absolute	0.534 ± 0.011	0.534 ± 0.014	0.545 ± 0.010	0.541 ± 0.011	0.527 ± 0.011	0.486 ± 0.012**
Relative	2.61 ± 0.03	2.62 ± 0.05	2.74 ± 0.04	2.79 ± 0.06	2.74 ± 0.06	2.86 ± 0.07**
Thymus						
Absolute	0.250 ± 0.008	0.291 ± 0.016	0.246 ± 0.012	0.280 ± 0.022	0.290 ± 0.022	0.236 ± 0.015
Relative	1.22 ± 0.04	1.43 ± 0.08	1.24 ± 0.06	1.43 ± 0.11	1.50 ± 0.10	1.39 ± 0.10

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=7

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 3-Month Interim Evaluation in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	20,000 ppm
n	10	10
Necropsy body wt	344 ± 5	248 ± 6**
R. Kidney		
Absolute	1.231 ± 0.018	1.125 ± 0.026**
Relative	3.59 ± 0.05	4.55 ± 0.07**
Liver		
Absolute	13.762 ± 0.251	11.777 ± 0.287**
Relative	40.08 ± 0.70	47.56 ± 0.27**

** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	9	7	9	5
Necropsy body wt	456 ± 7	453 ± 14	434 ± 9	407 ± 14**
R. Kidney				
Absolute	1.630 ± 0.032	1.603 ± 0.073	1.599 ± 0.041	1.808 ± 0.154
Relative	3.58 ± 0.08	3.54 ± 0.12	3.69 ± 0.09	4.49 ± 0.50**
Liver				
Absolute	15.861 ± 0.165	16.123 ± 0.590	16.604 ± 0.668	15.248 ± 0.603
Relative	34.86 ± 0.59	35.62 ± 1.06	38.24 ± 1.09*	37.42 ± 0.63*
Female				
n	10	9	7	8
Necropsy body wt	297 ± 5	276 ± 6	279 ± 7	281 ± 8
R. Kidney				
Absolute	0.949 ± 0.020	0.924 ± 0.032	0.931 ± 0.025	0.980 ± 0.031
Relative	3.20 ± 0.04	3.35 ± 0.10	3.34 ± 0.05	3.49 ± 0.05**
Liver				
Absolute	8.535 ± 0.190	8.446 ± 0.173	8.624 ± 0.082	9.213 ± 0.366
Relative	28.76 ± 0.33	30.63 ± 0.43**	30.97 ± 0.71**	32.77 ± 0.59**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
n	10	8	10	10	10	7
Necropsy body wt	27.8 ± 1.6	28.0 ± 1.2	27.5 ± 1.0	25.4 ± 0.4	21.6 ± 0.4**	17.4 ± 0.4**
Brain						
Absolute	0.493 ± 0.007	0.465 ± 0.009*	0.465 ± 0.009*	0.486 ± 0.005	0.467 ± 0.004*	0.467 ± 0.008
Relative	18.47 ± 1.50	16.82 ± 0.80	17.14 ± 0.72	19.20 ± 0.36	21.63 ± 0.43**	26.82 ± 0.36**
Heart						
Absolute	0.171 ± 0.005	0.163 ± 0.010	0.170 ± 0.008	0.172 ± 0.009	0.146 ± 0.007*	0.132 ± 0.006**
Relative	6.51 ± 0.75	5.87 ± 0.42	6.23 ± 0.26	6.78 ± 0.35	6.76 ± 0.28	7.58 ± 0.32
R. Kidney						
Absolute	0.284 ± 0.005	0.251 ± 0.004*	0.261 ± 0.006*	0.257 ± 0.007*	0.227 ± 0.007**	0.199 ± 0.016**
Relative	10.63 ± 0.82	9.07 ± 0.35	9.60 ± 0.42	10.15 ± 0.26	10.47 ± 0.23	11.43 ± 0.88
Liver						
Absolute	1.410 ± 0.035	1.405 ± 0.051	1.374 ± 0.037	1.397 ± 0.032	1.114 ± 0.052**	0.948 ± 0.049**
Relative	52.87 ± 4.54	50.36 ± 0.97	50.56 ± 2.26	55.05 ± 1.09	51.27 ± 1.71	54.34 ± 2.60
Lungs						
Absolute	0.179 ± 0.007	0.176 ± 0.005	0.175 ± 0.005	0.194 ± 0.013	0.163 ± 0.005	0.163 ± 0.011
Relative	6.84 ± 0.88	6.35 ± 0.29	6.40 ± 0.19	7.62 ± 0.46	7.56 ± 0.20	9.38 ± 0.65**
Spleen						
Absolute	0.063 ± 0.001	0.059 ± 0.003	0.060 ± 0.003	0.058 ± 0.003	0.041 ± 0.002**	0.040 ± 0.007**
Relative	2.35 ± 0.16	2.11 ± 0.09	2.20 ± 0.14	2.26 ± 0.08	1.88 ± 0.07	2.27 ± 0.38
R. Testis						
Absolute	0.122 ± 0.003	0.120 ± 0.002	0.129 ± 0.004[b]	0.122 ± 0.004	0.114 ± 0.002	0.102 ± 0.005**
Relative	4.59 ± 0.42	4.32 ± 0.16	4.97 ± 0.31[b]	4.82 ± 0.17	5.31 ± 0.15	5.84 ± 0.19**
Thymus						
Absolute	0.039 ± 0.003	0.036 ± 0.003	0.050 ± 0.004	0.039 ± 0.003	0.026 ± 0.003**	0.020 ± 0.004**
Relative	1.49 ± 0.21	1.32 ± 0.15	1.83 ± 0.17	1.51 ± 0.11	1.17 ± 0.13	1.16 ± 0.25

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female						
n	9	9	9	9	9	9
Necropsy body wt	25.8 ± 1.1	25.2 ± 0.9	23.7 ± 1.0	23.9 ± 0.7	18.5 ± 0.3**	16.0 ± 0.6**
Brain						
Absolute	0.488 ± 0.004	0.494 ± 0.002	0.493 ± 0.007	0.496 ± 0.007	0.478 ± 0.004	0.457 ± 0.006**
Relative	19.17 ± 0.83	19.82 ± 0.67	21.04 ± 0.78	20.88 ± 0.64	25.88 ± 0.32**	28.85 ± 1.15**
Heart						
Absolute	0.143 ± 0.005	0.154 ± 0.005	0.149 ± 0.006	0.147 ± 0.005	0.119 ± 0.001**	0.106 ± 0.003**
Relative	5.62 ± 0.29	6.20 ± 0.35	6.31 ± 0.22	6.18 ± 0.24	6.45 ± 0.10*	6.70 ± 0.30**
R. Kidney						
Absolute	0.190 ± 0.006	0.193 ± 0.004	0.191 ± 0.004	0.180 ± 0.004	0.171 ± 0.002**	0.154 ± 0.004**
Relative	7.40 ± 0.14	7.73 ± 0.31	8.13 ± 0.23	7.59 ± 0.29	9.24 ± 0.10**	9.68 ± 0.39**
Liver						
Absolute	1.241 ± 0.045	1.316 ± 0.027	1.212 ± 0.050	1.194 ± 0.032	0.989 ± 0.018**	0.863 ± 0.059**
Relative	48.30 ± 1.19	52.68 ± 1.59	51.45 ± 1.98	50.15 ± 1.53	53.57 ± 1.30	54.12 ± 3.44
Lungs						
Absolute	0.186 ± 0.016	0.186 ± 0.013	0.185 ± 0.003	0.178 ± 0.007	0.153 ± 0.005	0.168 ± 0.016
Relative	7.17 ± 0.41	7.54 ± 0.74	7.95 ± 0.42	7.44 ± 0.24	8.29 ± 0.24	10.72 ± 1.23**
Spleen						
Absolute	0.076 ± 0.003	0.075 ± 0.002	0.073 ± 0.005	0.070 ± 0.005	0.052 ± 0.002**	0.037 ± 0.004**
Relative	2.96 ± 0.10	3.01 ± 0.12	3.10 ± 0.17	2.94 ± 0.19	2.78 ± 0.12	2.31 ± 0.26*
Thymus						
Absolute	0.052 ± 0.005	0.052 ± 0.004	0.044 ± 0.004	0.046 ± 0.004	0.036 ± 0.004*	0.025 ± 0.004**
Relative	2.04 ± 0.20	2.07 ± 0.17	1.82 ± 0.13	1.91 ± 0.16	1.94 ± 0.23	1.54 ± 0.24

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=7

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
n	10	9	10	10
Necropsy body wt	48.6 ± 1.2	49.3 ± 1.9	47.6 ± 1.3	46.6 ± 1.5
R. Kidney				
Absolute	0.442 ± 0.012	0.434 ± 0.025	0.414 ± 0.013	0.423 ± 0.015
Relative	9.09 ± 0.12	8.82 ± 0.38	8.77 ± 0.38	9.13 ± 0.37
Liver				
Absolute	2.355 ± 0.192	2.271 ± 0.187	2.123 ± 0.155	2.313 ± 0.331
Relative	48.48 ± 3.72	45.71 ± 2.73	45.02 ± 3.92	50.75 ± 8.67
Female				
n	8	10	9	10
Necropsy body wt	50.4 ± 2.9	54.8 ± 1.7	52.7 ± 2.1	49.3 ± 2.0
R. Kidney				
Absolute	0.264 ± 0.009	0.253 ± 0.007	0.261 ± 0.005	0.263 ± 0.009
Relative	5.30 ± 0.20	4.65 ± 0.18	5.00 ± 0.18	5.38 ± 0.20
Liver				
Absolute	1.616 ± 0.074	1.678 ± 0.045	1.949 ± 0.211	1.741 ± 0.072
Relative	32.28 ± 0.73	30.80 ± 0.90	36.88 ± 3.25	35.70 ± 1.77

[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
CLINICAL CHEMISTRY AND URINALYSIS RESULTS

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Core Study						
Male						
Clinical Chemistry						
n	10	10	9	10	10	10
Urea nitrogen (mg/dL)	21.4 ± 0.6	22.8 ± 0.6	22.3 ± 1.4	21.7 ± 0.9	21.2 ± 0.7	21.2 ± 0.9
Creatinine (mg/dL)	0.80 ± 0.13	0.70 ± 0.15	0.89 ± 0.11	1.00 ± 0.00	0.90 ± 0.10	1.00 ± 0.00
Glucose (mg/dL)	98 ± 6	123 ± 8	132 ± 17	100 ± 5	108 ± 7	106 ± 8
Total protein (g/dL)	7.0 ± 0.1	6.9 ± 0.1	6.6 ± 0.3[b]	6.9 ± 0.1	7.0 ± 0.1	7.1 ± 0.1
Albumin (g/dL)	5.5 ± 0.1	5.4 ± 0.1	5.4 ± 0.0[c]	5.4 ± 0.1	5.4 ± 0.1	5.5 ± 0.1
Globulin (g/dL)	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1[c]	1.5 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
A/G ratio	3.8 ± 0.2	3.5 ± 0.2	3.9 ± 0.2[c]	3.7 ± 0.2	3.4 ± 0.1	3.6 ± 0.2
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)	0.156 ± 0.015	0.150 ± 0.016	0.170 ± 0.012	0.156 ± 0.018[d]	0.161 ± 0.006	0.148 ± 0.012
Protein (mg/hr)	0.658 ± 0.058	0.620 ± 0.057	0.728 ± 0.037	0.606 ± 0.127[d]	0.861 ± 0.036*	0.839 ± 0.044*
Volume (mL/16 hr)	8.2 ± 0.8	9.6 ± 1.5	12.3 ± 1.6	13.1 ± 2.9	19.5 ± 1.9**	17.7 ± 1.5**
Specific gravity	1.029 ± 0.003	1.024 ± 0.003	1.023 ± 0.003	1.015 ± 0.003**	1.016 ± 0.001**	1.015 ± 0.001**
Female						
Clinical Chemistry						
n	10	10	9	8	10	10
Urea nitrogen (mg/dL)	20.9 ± 1.0	21.6 ± 0.4	20.8 ± 0.7	20.8 ± 0.9	20.0 ± 0.7	21.5 ± 0.6
Creatinine (mg/dL)	0.90 ± 0.10	0.90 ± 0.10	1.00 ± 0.00	0.63 ± 0.18	0.50 ± 0.17	0.70 ± 0.15
Glucose (mg/dL)	90 ± 5	100 ± 6	104 ± 11	98 ± 5	90 ± 3	108 ± 9
Total protein (g/dL)	7.1 ± 0.1	7.0 ± 0.1	6.8 ± 0.0	6.6 ± 0.1*	6.8 ± 0.1*	6.4 ± 0.1**
Albumin (g/dL)	5.6 ± 0.1	5.6 ± 0.1	5.3 ± 0.1**	5.3 ± 0.1**	5.4 ± 0.1**	5.2 ± 0.1**
Globulin (g/dL)	1.4 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.2 ± 0.1
A/G ratio	4.1 ± 0.2	3.9 ± 0.1	3.5 ± 0.2	4.0 ± 0.3	3.8 ± 0.2	4.5 ± 0.3
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)	0.091 ± 0.006	0.073 ± 0.009[d]	0.089 ± 0.006	0.089 ± 0.009	0.094 ± 0.008	0.100 ± 0.012
Protein (mg/hr)	0.037 ± 0.003[d]	0.029 ± 0.004[d]	0.035 ± 0.004	0.032 ± 0.002	0.043 ± 0.003	0.040 ± 0.008
Volume (mL/16 hr)	6.0 ± 0.6	10.2 ± 2.1	10.3 ± 1.0*	8.8 ± 0.8	9.7 ± 1.3	9.9 ± 2.1
Specific gravity	1.031 ± 0.005	1.020 ± 0.006	1.016 ± 0.002*	1.020 ± 0.002	1.020 ± 0.003	1.022 ± 0.004
Special Study						
Male						
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	30.4 ± 1.0[c]	31.8 ± 1.1[c]	29.6 ± 1.2[c]	30.1 ± 1.3	32.0 ± 1.5	32.3 ± 1.1
Day 15	26.2 ± 1.0	26.9 ± 0.9	25.4 ± 0.8	24.9 ± 0.8	28.8 ± 1.2	25.3 ± 0.9
Day 30	26.5 ± 0.4	26.7 ± 1.0	22.4 ± 0.7*	18.5 ± 0.7**	23.7 ± 0.9	27.4 ± 0.7
Day 60	30.9 ± 1.0[c]	23.1 ± 0.8**	25.1 ± 0.8	25.3 ± 1.0[b]	22.3 ± 1.7**[c]	28.6 ± 3.7
Week 13	24.5 ± 1.1[b]	22.3 ± 0.8[b]	23.0 ± 0.5[c]	22.4 ± 1.4[c]	17.9 ± 1.7**[c]	23.6 ± 0.9

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Male (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Creatinine (mg/dL)						
Day 3	0.60 ± 0.16	0.33 ± 0.17[c]	0.33 ± 0.17[c]	0.20 ± 0.13	0.70 ± 0.15	0.60 ± 0.16
Day 15	0.30 ± 0.15	0.10 ± 0.10	0.50 ± 0.17	0.80 ± 0.13	0.50 ± 0.17	0.40 ± 0.16
Day 30	0.70 ± 0.15	0.60 ± 0.16	0.70 ± 0.15	0.30 ± 0.15	0.50 ± 0.17	0.70 ± 0.15
Day 60	0.78 ± 0.15[c]	0.89 ± 0.11[c]	0.90 ± 0.10	0.75 ± 0.16[b]	0.57 ± 0.20[c]	0.50 ± 0.17
Week 13	0.88 ± 0.13[b]	1.00 ± 0.00[b]	1.00 ± 0.00[c]	0.86 ± 0.14[c]	0.89 ± 0.11[c]	0.89 ± 0.11[c]
Glucose (mg/dL)						
Day 3	170 ± 7	166 ± 8[c]	180 ± 7[c]	178 ± 8	201 ± 8**	186 ± 7*
Day 15	190 ± 10	184 ± 9	174 ± 7	175 ± 7	168 ± 5	149 ± 6**
Day 30	170 ± 12	166 ± 5	160 ± 5	155 ± 4	174 ± 9	149 ± 7
Day 60	203 ± 21[c]	158 ± 15	219 ± 19	163 ± 18[b]	187 ± 14[b]	155 ± 18
Week 13	150 ± 20[b]	146 ± 11[b]	160 ± 8[c]	196 ± 23[c]	175 ± 16[c]	154 ± 17
Total protein (g/dL)						
Day 3	5.2 ± 0.1[c]	5.1 ± 0.1[b]	5.6 ± 0.1**[c]	5.7 ± 0.1**	5.7 ± 0.1**	5.7 ± 0.1**
Day 15	5.9 ± 0.1	5.9 ± 0.1	6.1 ± 0.1	6.2 ± 0.1	6.3 ± 0.0**	6.3 ± 0.1**
Day 30	6.4 ± 0.1	6.5 ± 0.1	6.1 ± 0.1	6.4 ± 0.1	6.4 ± 0.1	6.4 ± 0.1
Day 60	6.5 ± 0.1[c]	6.2 ± 0.2[c]	6.6 ± 0.1[c]	6.9 ± 0.1*[b]	6.8 ± 0.1[e]	7.0 ± 0.1**
Week 13	7.0 ± 0.1[b]	7.1 ± 0.1[b]	6.8 ± 0.1[c]	7.0 ± 0.1[c]	7.0 ± 0.1[b]	6.9 ± 0.1[b]
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)						
Day 3	0.083 ± 0.004	0.075 ± 0.004	0.077 ± 0.005	0.078 ± 0.003	0.080 ± 0.004	0.065 ± 0.006
Day 15	0.138 ± 0.006[c]	0.136 ± 0.007	0.118 ± 0.007	0.146 ± 0.010[c]	0.156 ± 0.007	0.120 ± 0.009[c]
Day 30	0.165 ± 0.010	0.118 ± 0.006**	0.156 ± 0.005	0.183 ± 0.011	0.148 ± 0.007	0.155 ± 0.009
Day 60	0.196 ± 0.013	0.179 ± 0.003	0.156 ± 0.004**	0.156 ± 0.009*[c]	0.144 ± 0.006**	0.140 ± 0.008**
Week 13	0.184 ± 0.018[c]	0.177 ± 0.009[c]	0.154 ± 0.007[c]	0.162 ± 0.011[b]	0.136 ± 0.007*	0.129 ± 0.012*[b]
Protein (mg/hr)						
Day 3	0.071 ± 0.011	0.059 ± 0.009	0.069 ± 0.007	0.064 ± 0.007	0.068 ± 0.005	0.050 ± 0.006
Day 15	0.606 ± 0.032[c]	0.410 ± 0.054*	0.522 ± 0.047	0.544 ± 0.045[c]	0.450 ± 0.023**	0.168 ± 0.018**[c]
Day 30	0.797 ± 0.046	0.627 ± 0.039*	0.645 ± 0.041*	0.655 ± 0.029*	0.598 ± 0.034**	0.438 ± 0.026**
Day 60	0.637 ± 0.051	0.727 ± 0.036	0.754 ± 0.021	0.679 ± 0.047[c]	0.749 ± 0.049	0.820 ± 0.039*
Week 13	0.644 ± 0.050[c]	0.766 ± 0.058[c]	0.668 ± 0.038[c]	0.743 ± 0.059[b]	0.756 ± 0.055[c]	0.670 ± 0.073[b]
Volume (mL/16 hr)						
Day 3	10.3 ± 1.1	10.3 ± 1.3	9.0 ± 1.4	10.7 ± 1.2	8.9 ± 0.9	6.4 ± 0.9*
Day 15	17.7 ± 1.9[c]	12.8 ± 2.0	10.9 ± 1.4	14.7 ± 2.2	16.3 ± 1.1	7.4 ± 1.3**[c]
Day 30	14.4 ± 1.5	14.5 ± 1.8	9.1 ± 0.9*	12.2 ± 1.2	17.5 ± 1.9	18.5 ± 2.1
Day 60	14.2 ± 2.1	14.7 ± 1.9	14.0 ± 1.8	19.2 ± 2.7[c]	25.9 ± 1.9**	28.7 ± 3.1**
Week 13	16.2 ± 2.1[c]	13.3 ± 1.7[c]	11.8 ± 1.8[c]	16.9 ± 2.9[b]	24.5 ± 2.3	27.8 ± 3.5*[b]
Specific gravity						
Day 3	1.012 ± 0.001	1.011 ± 0.001	1.015 ± 0.002	1.012 ± 0.001	1.013 ± 0.001	1.016 ± 0.002
Day 15	1.021 ± 0.010[c]	1.018 ± 0.003	1.017 ± 0.001	1.015 ± 0.003	1.015 ± 0.001	1.026 ± 0.003**[c]
Day 30	1.018 ± 0.002	1.014 ± 0.002	1.025 ± 0.002	1.022 ± 0.002	1.014 ± 0.001	1.014 ± 0.001
Day 60	1.023 ± 0.002	1.018 ± 0.003	1.017 ± 0.002	1.014 ± 0.002*[c]	1.009 ± 0.001**	1.010 ± 0.001**
Week 13	1.017 ± 0.003[c]	1.021 ± 0.003[c]	1.020 ± 0.003[c]	1.016 ± 0.002[b]	1.010 ± 0.002*	1.009 ± 0.001*[b]

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Male (continued)						
Urine Concentration Study						
n	8	8	6	5	10	10
Volume (mL/4 hr)						
Day 4	1.600 ± 0.400[f]	1.567 ± 0.343[e]	0.458 ± 0.042**	1.000 ± 0.274*	0.563 ± 0.157*[g]	0.417 ± 0.083**[h]
Day 16	1.929 ± 0.352[c]	2.313 ± 0.499	0.700 ± 0.122*[f]	1.222 ± 0.222[c]	1.150 ± 0.107	0.850 ± 0.130*
Day 31	0.600 ± 0.158	1.229 ± 0.276[c]	0.875 ± 0.183[b]	1.100 ± 0.258[e]	0.786 ± 0.101[c]	1.233 ± 0.245[c]
Day 61	1.188 ± 0.188	1.188 ± 0.210	1.667 ± 0.511	0.486 ± 0.212[c]	1.150 ± 0.130	1.300 ± 0.153
Week 13	0.650 ± 0.218[g]	0.814 ± 0.314[c]	0.260 ± 0.098[f]	0.800 ± 0.200	0.167 ± 0.067[e]	0.789 ± 0.201[c]
Specific gravity						
Day 4	1.023 ± 0.008[g]	1.015 ± 0.009[g]	1.040 ± 0.003	1.035 ± 0.029[i]	1.050 ± 0.007[g]	1.071 ± 0.009*[h]
Day 16	1.039 ± 0.010[c]	1.037 ± 0.010	1.065 ± 0.008[f]	1.047 ± 0.008[c]	1.057 ± 0.002	1.067 ± 0.003**
Day 31	1.063 ± 0.005	1.026 ± 0.006**[c]	1.060 ± 0.005[b]	1.053 ± 0.006[e]	1.056 ± 0.006[b]	1.047 ± 0.003[c]
Day 61	1.067 ± 0.006	1.070 ± 0.003	1.058 ± 0.012	1.053 ± 0.008[c]	1.059 ± 0.003	1.047 ± 0.003**
Week 13	1.058 ± 0.009[g]	1.056 ± 0.010[c]	1.056 ± 0.010	1.043 ± 0.007	1.063 ± 0.003[e]	1.036 ± 0.005[c]
Female						
Clinical Chemistry						
n	9	10	9	10	10	10
Urea nitrogen (mg/dL)						
Day 3	31.2 ± 1.7	31.4 ± 1.7	33.1 ± 1.9	32.3 ± 1.3	32.0 ± 0.7	28.9 ± 1.2
Day 15	33.2 ± 0.9	31.7 ± 0.6	33.9 ± 1.2	34.8 ± 1.6	28.7 ± 0.6**	27.7 ± 0.7**
Day 30	25.8 ± 0.9	24.6 ± 0.5	28.7 ± 0.7	24.7 ± 1.1	24.3 ± 0.9	23.9 ± 0.9
Day 60	26.7 ± 1.0	24.8 ± 0.7	29.9 ± 1.0	29.6 ± 0.6	27.4 ± 1.3[c]	25.5 ± 1.1
Week 13	28.1 ± 0.7	28.7 ± 1.0	28.9 ± 1.2	27.6 ± 0.7	25.6 ± 0.8[c]	26.6 ± 0.9
Creatinine (mg/dL)						
Day 3	0.44 ± 0.18	0.10 ± 0.10	0.44 ± 0.18	0.30 ± 0.15	0.00 ± 0.00	0.00 ± 0.00
Day 15	0.22 ± 0.15	0.20 ± 0.13	0.67 ± 0.17	0.70 ± 0.15	0.30 ± 0.15	0.30 ± 0.15
Day 30	1.00 ± 0.00	0.60 ± 0.16*	0.56 ± 0.18*	0.60 ± 0.16	0.40 ± 0.16**	0.10 ± 0.10**
Day 60	0.78 ± 0.15	0.70 ± 0.15	1.00 ± 0.00	1.00 ± 0.00[c]	0.78 ± 0.15[c]	0.90 ± 0.10
Week 13	1.00 ± 0.00	0.90 ± 0.10	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00[c]	0.90 ± 0.10
Glucose (mg/dL)						
Day 3	175 ± 28	216 ± 33	155 ± 6	159 ± 5	153 ± 8	167 ± 6
Day 15	167 ± 6	159 ± 7	157 ± 9	157 ± 10	142 ± 8**	144 ± 7**
Day 30	146 ± 4	149 ± 4	135 ± 8	155 ± 5	145 ± 10	140 ± 4
Day 60	140 ± 8	143 ± 4	187 ± 20*	194 ± 12**	205 ± 18**[c]	177 ± 14**
Week 13	148 ± 6	153 ± 4	150 ± 10	169 ± 11	147 ± 6[c]	166 ± 13
Total protein (g/dL)						
Day 3	5.9 ± 0.1	6.2 ± 0.1	5.9 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	5.7 ± 0.1
Day 15	5.8 ± 0.1	5.9 ± 0.2	6.1 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	5.9 ± 0.1
Day 30	5.9 ± 0.1	6.0 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	5.8 ± 0.1
Day 60	6.7 ± 0.1	6.7 ± 0.0	6.7 ± 0.1	6.5 ± 0.1[c]	6.8 ± 0.1[c]	6.6 ± 0.1
Week 13	6.9 ± 0.1	6.7 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	6.7 ± 0.1[c]	6.4 ± 0.1**

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Female (continued)						
Urinalysis						
n	9	10	9	10	10	10
Glucose (mg/hr)						
Day 3	0.088 ± 0.005	0.088 ± 0.006	0.079 ± 0.005[j]	0.093 ± 0.010	0.059 ± 0.003**	0.053 ± 0.003**
Day 15	0.072 ± 0.005	0.074 ± 0.007[c]	0.065 ± 0.006	0.062 ± 0.007[c]	0.086 ± 0.006	0.081 ± 0.005
Day 30	0.094 ± 0.004	0.085 ± 0.004	0.122 ± 0.018[b]	0.107 ± 0.012	0.091 ± 0.012	0.105 ± 0.005
Day 60	0.109 ± 0.009	0.097 ± 0.010	0.091 ± 0.005[b]	0.078 ± 0.005**	0.076 ± 0.004**	0.091 ± 0.006*
Week 13	0.098 ± 0.008	0.096 ± 0.005	—[k]	0.077 ± 0.004	0.077 ± 0.002[c]	0.088 ± 0.005
Protein (mg/hr)						
Day 3	0.028 ± 0.002	0.027 ± 0.002	0.030 ± 0.004[j]	0.030 ± 0.002	0.030 ± 0.003	0.025 ± 0.002
Day 15	0.033 ± 0.004	0.031 ± 0.003[c]	0.031 ± 0.004	0.038 ± 0.005[c]	0.033 ± 0.002	0.033 ± 0.002
Day 30	0.030 ± 0.002[b]	0.034 ± 0.003	0.033 ± 0.007[b]	0.029 ± 0.003	0.034 ± 0.004	0.039 ± 0.004[c]
Day 60	0.033 ± 0.002	0.035 ± 0.005[c]	0.044 ± 0.004[b]	0.041 ± 0.003	0.035 ± 0.005	0.044 ± 0.006
Week 13	0.055 ± 0.006	0.047 ± 0.003	—	0.039 ± 0.004	0.038 ± 0.004[c]	0.041 ± 0.003
Volume (mL/16 hr)						
Day 3	13.2 ± 2.1[j]	13.2 ± 1.2	13.5 ± 1.5[j]	15.7 ± 2.4	14.6 ± 1.0	6.7 ± 1.0*
Day 15	11.9 ± 1.7	10.2 ± 1.7	10.8 ± 1.4	13.7 ± 2.9[c]	12.6 ± 1.5	11.8 ± 1.1
Day 30	12.8 ± 1.2	12.0 ± 1.6	13.1 ± 1.4	10.0 ± 2.2	14.4 ± 1.2	12.7 ± 1.6
Day 60	10.2 ± 1.4	10.4 ± 1.6	14.1 ± 1.9[b]	14.0 ± 2.3	11.8 ± 1.4	14.7 ± 1.2
Week 13	8.9 ± 1.0	11.3 ± 1.4	—	13.4 ± 1.5	12.7 ± 2.0[c]	11.0 ± 1.2
Specific gravity						
Day 3	1.011 ± 0.002[j]	1.008 ± 0.001	1.017 ± 0.010[j]	1.008 ± 0.001	1.008 ± 0.000	1.017 ± 0.002
Day 15	1.013 ± 0.001	1.016 ± 0.003	1.014 ± 0.002	1.015 ± 0.003[c]	1.015 ± 0.002	1.016 ± 0.002
Day 30	1.012 ± 0.001	1.013 ± 0.001	1.016 ± 0.002	1.026 ± 0.006	1.012 ± 0.001	1.016 ± 0.002
Day 60	1.018 ± 0.002	1.017 ± 0.002	1.012 ± 0.001**[b]	1.016 ± 0.004*	1.013 ± 0.002*	1.012 ± 0.001*
Week 13	1.018 ± 0.002	1.015 ± 0.001	—	1.011 ± 0.001**	1.013 ± 0.001[c]	1.015 ± 0.001
Urine Concentration Study						
n	5	4	5	6	7	9
Volume (mL/4 hr)						
Day 4	0.900 ± 0.100	0.750 ± 0.144	0.600 ± 0.100*	0.700 ± 0.122[f]	0.643 ± 0.092*	0.611 ± 0.073*
Day 16	0.371 ± 0.123[c]	0.280 ± 0.092[f]	0.586 ± 0.120[c]	0.588 ± 0.134[b]	0.917 ± 0.201*[e]	0.789 ± 0.140*
Day 31	0.500 ± 0.000[g]	0.625 ± 0.125	0.833 ± 0.167[h]	1.333 ± 0.333**	0.571 ± 0.118	0.944 ± 0.227
Day 61	0.100 ± 0.000[h]	0.400 ± 0.125[c]	0.340 ± 0.098	0.467 ± 0.088*[c]	0.167 ± 0.067[e]	0.383 ± 0.147[e]
Week 13	0.680 ± 0.461	0.100 ± 0.000**[f]	0.550 ± 0.450[i]	0.183 ± 0.065	0.788 ± 0.234[b]	1.100 ± 0.187*[f]
Specific gravity						
Day 4	1.066 ± 0.004	1.076 ± 0.004	1.067 ± 0.005	1.064 ± 0.011[f]	1.077 ± 0.003	1.064 ± 0.006
Day 16	1.074 ± 0.003[c]	1.075 ± 0.003[f]	1.068 ± 0.005[c]	1.055 ± 0.010[b]	1.047 ± 0.009[e]	1.060 ± 0.006
Day 31	1.061 ± 0.013	1.067 ± 0.007	1.060 ± 0.013[h]	1.053 ± 0.009	1.067 ± 0.008	1.054 ± 0.008
Day 61	1.072 ± 0.004[h]	1.033 ± 0.009**[c]	1.062 ± 0.006	1.050 ± 0.006[c]	1.046 ± 0.011[e]	1.063 ± 0.004[e]
Week 13	1.048 ± 0.014	1.037 ± 0.009[e]	1.035 ± 0.010[i]	1.048 ± 0.008[c]	1.059 ± 0.007[b]	1.061 ± 0.008[f]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8 [c] n=7 [d] n=9 [e] n=6 [f] n=5 [g] n=4 [h] n=3 [i] n=2 [j] n=10
[k] No measurements taken at this exposure level

TABLE G2
Clinical Chemistry and Urinalysis Data for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
Clinical Chemistry						
n	6	8	9	7	8	5
Urea nitrogen (mg/dL)	32.0 ± 3.6[b]	24.6 ± 1.5	28.0 ± 1.5	35.8 ± 2.9[c]	46.4 ± 5.9	72.3 ± 15.1*[d]
Glucose (mg/dL)	123 ± 8[b]	146 ± 14	162 ± 12	162 ± 14[c]	141 ± 18	146 ± 18[d]
Total protein (g/dL)	5.8 ± 0.1	5.9 ± 0.1	5.5 ± 0.2	5.8 ± 0.1[e]	5.7 ± 0.1	5.8 ± 0.2[d]
Albumin (g/dL)	3.8 ± 0.1	4.0 ± 0.1	3.6 ± 0.2	3.8 ± 0.1	3.8 ± 0.1	4.0 ± 0.2
Globulin (g/dL)	2.0 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1
A/G ratio	1.9 ± 0.1	2.1 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	2.1 ± 0.2
Urinalysis						
n	4	3	9	10	10	4
Glucose (mg/hr)	0.051 ± 0.014	0.024 ± 0.011	0.036 ± 0.007	0.025 ± 0.004	0.038 ± 0.004[c]	0.034 ± 0.004
Protein (mg/hr)	0.364 ± 0.062	0.148 ± 0.065	0.264 ± 0.051	0.228 ± 0.045	0.166 ± 0.028*	0.075 ± 0.020**
Volume (mL/24 hr)	3.63 ± 0.80	4.17 ± 1.69	3.06 ± 0.55	2.72 ± 0.55[c]	2.00 ± 0.17	2.25 ± 0.43
Specific gravity	1.020 ± 0.004	1.005 ± 0.003	1.016 ± 0.003	1.017 ± 0.004	1.023 ± 0.002	1.018 ± 0.001
Female						
Clinical Chemistry						
n	9	7	9	7	8	5
Urea nitrogen (mg/dL)	21.9 ± 0.9	24.8 ± 2.7[e]	22.6 ± 1.4	26.0 ± 3.0[e]	27.6 ± 1.7*[c]	37.8 ± 3.1**
Glucose (mg/dL)	151 ± 10	182 ± 13[e]	151 ± 7	148 ± 8[e]	130 ± 11[c]	118 ± 23
Total protein (g/dL)	6.0 ± 0.1	5.8 ± 0.1	6.4 ± 0.1	6.1 ± 0.1	6.1 ± 0.1[c]	6.4 ± 0.2
Albumin (g/dL)	4.2 ± 0.1	4.0 ± 0.1	4.5 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.1
Globulin (g/dL)	1.8 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	2.0 ± 0.2
A/G ratio	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.5 ± 0.2	2.3 ± 0.3
Urinalysis						
n	9	7	7	9	9	6
Glucose (mg/hr)	0.043 ± 0.005	0.039 ± 0.005	0.041 ± 0.009	0.044 ± 0.009	0.048 ± 0.005	0.022 ± 0.005
Protein (mg/hr)	0.147 ± 0.027	0.171 ± 0.024	0.154 ± 0.037	0.161 ± 0.027	0.112 ± 0.011	0.016 ± 0.003**
Volume (mL/24 hr)	3.7 ± 0.5	3.4 ± 0.6	3.5 ± 0.8	3.0 ± 0.6	3.5 ± 0.3	2.2 ± 0.6
Specific gravity	1.016 ± 0.002	1.016 ± 0.002	1.016 ± 0.002	1.020 ± 0.003	1.018 ± 0.002	1.008 ± 0.002

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=7
[c] n=9
[d] n=6
[e] n=8

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt.	334 ± 6	308 ± 10*	299 ± 8**	255 ± 7**
R. cauda	0.169 ± 0.011	0.166 ± 0.007	0.175 ± 0.008	0.162 ± 0.008
R. epididymis	0.509 ± 0.016	0.519 ± 0.024	0.508 ± 0.020	0.503 ± 0.016
R. testis	1.492 ± 0.027	1.443 ± 0.035	1.411 ± 0.038	1.360 ± 0.036**
Epididymal spermatozoal parameters				
Motility (%)	97.33 ± 0.78	97.03 ± 0.71	97.48 ± 0.53	96.96 ± 1.05
Concentration (10^6/g cauda epididymal tissue)	558.2 ± 42.8	524.6 ± 27.3	552.0 ± 32.1	646.8 ± 50.7
Normal (per 500 sperm)	496.3 ± 0.5	495.7 ± 0.4	493.9 ± 1.4	495.4 ± 0.6
Abnormal (%)	0.740 ± 0.099	0.860 ± 0.079	1.220 ± 0.284	0.920 ± 0.116
Amorphous (per 500 sperm)	0.300 ± 0.153	0.500 ± 0.224	0.600 ± 0.221	0.600 ± 0.221
Excessive hook (per 500 sperm)	1.400 ± 0.476	0.900 ± 0.379	1.500 ± 0.764	1.500 ± 0.269
No hook (per 500 sperm)	1.20 ± 0.25	2.30 ± 0.47	3.10 ± 0.82	1.70 ± 0.33
Pin-head (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Short-headed (per 500 sperm)	0.800 ± 0.249	0.500 ± 0.167	0.900 ± 0.277	0.800 ± 0.200
Two tails or heads (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Female				
n	10	10	10	10
Necropsy body wt. (g)	200 ± 6	184 ± 3**	174 ± 6**	163 ± 2**
Estrous cycle length (days)	4.70 ± 0.21	4.70 ± 0.15	5.00 ± 0.15	5.56 ± 0.47[b]
Estrous stages (% of cycle)				
Diestrus	27.1	28.6	27.1	27.1
Proestrus	14.3	14.3	17.1	20.0
Estrus	27.1	27.1	21.4	21.4
Metestrus	31.4	30.0	34.3	31.4

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	10	10	10	7
Weights (g)				
Necropsy body wt. (g)	27.8 ± 1.6	25.4 ± 0.4	21.6 ± 0.4**	17.4 ± 0.4**
R. cauda	0.023 ± 0.001	0.020 ± 0.002	0.017 ± 0.001**	0.012 ± 0.001**
R. epididymis	0.086 ± 0.005	0.074 ± 0.005	0.055 ± 0.002**	0.048 ± 0.003**
R. testis	0.122 ± 0.003	0.122 ± 0.004	0.114 ± 0.002	0.102 ± 0.005**
Epididymal spermatozoal parameters				
Motility (%)	90.17 ± 0.93	92.96 ± 2.12	90.05 ± 1.74	85.79 ± 9.36
Concentration (10^6/g cauda epididymal tissue)	988.1 ± 64.0	1,065.3 ± 110	1,163.2 ± 116	1,334.8 ± 157
Normal (per 500 sperm)	494.7 ± 0.7	494.2 ± 1.1	494.4 ± 0.8	495.1 ± 0.9
Abnormal (%)	1.060 ± 0.140	1.160 ± 0.229	0.940 ± 0.133	0.971 ± 0.177
Amorphous (per 500 sperm)	2.50 ± 0.56	2.40 ± 1.01	1.90 ± 0.28	1.71 ± 0.52
Banana (per 500 sperm)	2.10 ± 0.28	2.30 ± 0.42	1.70 ± 0.47	2.43 ± 0.30
Blunt hook (per 500 sperm)	0.400 ± 0.267	0.500 ± 0.224	0.700 ± 0.396	0.143 ± 0.143
Pin-head (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.143 ± 0.143
Short-headed (per 500 sperm)	0.200 ± 0.133	0.200 ± 0.133	0.200 ± 0.133	0.143 ± 0.143
Two tails or heads (per 500 sperm)	0.000 ± 0.000	0.200 ± 0.133	0.100 ± 0.100	0.286 ± 0.286
Female				
n	9	9	9	9
Necropsy body wt. (g)	25.8 ± 1.1	23.9 ± 0.7	18.5 ± 0.3**	16.0 ± 0.6**
Estrous cycle length (days)	4.00 ± 0.00[b]	4.00 ± 0.00[c]	4.11 ± 0.11[c]	5.43 ± 0.48[b]
Estrous stages (% of cycle)				
Diestrus	32.9	22.9	20.0	25.7
Proestrus	18.6	21.4	12.9	12.9
Estrus	18.6	21.4	31.4	41.4
Metestrus	20.0	24.3	25.7	18.6
Unclear diagnosis	10.0	10.0	10.0	1.4

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 7 days or was unclear in 3 of 10 animals.
[c] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

2,2-Bis(bromomethyl)-1,3-propanediol was obtained from Dow Chemical Company (Rolling Meadows, IL) in one lot (840429-162), which was used during the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the 2,2-bis(bromomethyl)-1,3-propanediol studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a fine white powder, was identified as 2,2-bis(bromomethyl)-1,3-propanediol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of 2,2-bis(bromomethyl)-1,3-propanediol (Figures I1 and I2).

The purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography (TLC), and gas chromatography. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) toluene:methanol (80:20), and 2) chloroform:acetone (80:20) with 3-chloro-1,2-propanediol as a reference standard. Plates were examined under visible and ultraviolet light at 254 nm and 366 nm and with a spray of 0.5% potassium permanganate in 1N sodium hydroxide. Gas chromatography was performed using a flame ionization detector and a nitrogen carrier gas. Two systems were used:

A) Tenax GC 60/80 mesh column with a nitrogen flow rate of 17 mL/minute and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and

B) 3% SP-2250 on 100/120 Supelcoport column with a nitrogen flow rate of 70 mL/minute and an isothermal oven temperature of 195° C.

Elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values for 2,2-bis(bromomethyl)-1,3-propanediol. Karl Fischer water analysis indicated 0.3% ± 0.1% water. TLC by each system indicated a major spot and one impurity. Gas chromatography by system A indicated one major peak and three impurities with areas greater than or equal to 0.1%, and totaling 1.6% relative to the major peak. Gas chromatography using system B indicated a major peak and four impurities with areas greater than or equal to 0.1%, and totaling 3.0% relative to the major peak.

High-performance liquid chromatography (HPLC) analyses were also conducted. HPLC was performed using a DuPont Zorbax ODS column with an isocratic solvent system of water:methanol (25:75) at a flow rate of 1.0 mL/minute and indicated a major peak and nine impurities with areas greater than 0.1% and totaling 21.2%. Samples were also analyzed with solvent systems containing 80% and 100% methanol as well as methanol:water (30:70). No additional impurities with relative areas greater than 1% were observed.

Five impurity peaks with areas of 1% or greater were detected in lot 840429-162. The impurities were further characterized by HPLC and direct inlet mass spectrometry (DIMS). The major peak and four of the impurities with peak areas greater than 1% were isolated by HPLC as described above, but with a water:methanol (38:62) solvent system. These impurities were then characterized by analysis with DIMS with electron impact, positive chemical ionization, and negative chemical ionization. Two impurities, 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%) and 2,2,-bis(bromomethyl)-1-bromo-3-hydroxypropane (6.9%), were identified. One impurity (1%) was tentatively identified as a dimer of the

parent chemical. Another impurity peak (2.8%) consisted of multiple components, including a structural isomer and a dimer of the parent compound (Figure I3).

A specific quantitation for an identified impurity was performed if a standard was available. The impurity identified as 1,1-bis(bromomethyl)-1-bromo-3-hydroxypropane was quantitated against a standard obtained from Velsicol Chemical Company (Chicago, IL), by HPLC. HPLC as described previously, but with water:methanol (35:65) solvent system and velerophenone as an internal standard, indicated 7.5% ± 0.1% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane.

The impurity identified as pentaerythritol (reactant in the synthesis of 2,2-bis(bromomethyl)-1,3-propanediol) was quantitated against a pentaerythritol standard solution prepared by the analytical chemistry laboratory. HPLC as described with a water:methanol (25:75) solvent system detected a peak in the chromatographic profile of lot 840429-162 with a retention time that was consistent with that of the concomitantly analyzed pentaerythritol standard. Interference from the solvent was observed and the impurity peak could not be accurately quantitated. The amount of pentaerythritol observed was estimated at 0.2% by peak are comparison. The overall purity for lot 840429-162 was determined to be approximately 78.6%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Stability studies were performed using gas chromatography system B as described previously for the purity analysis, except with a carrier gas flow rate of 60 mL/minute and an isothermal oven temperature of 150° C. These studies indicated that 2,2-bis(bromomethyl)-1,3-propanediol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in sealed containers, protected from light. Stability was monitored monthly during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 13-week and 2-year feed studies were prepared weekly by mixing the appropriate quantities of dry 2,2-bis(bromomethyl)-1,3-propanediol with feed in a Udy® Cyclone Sample Mill to produce a premix. Premixes were then blended with more feed in a Patterson-Kelley Twin Shell® blender for 15 minutes, with an intensifier bar used for the initial 5 minutes. The formulations were stored in sealed, double plastic bags for no longer than 21 days (13-week studies) or 15 days (2-year studies) at −20° C.

Homogeneity and stability analyses of the dosed feed preparations were conducted by the analytical chemistry laboratory. For the homogeneity studies, samples of 630 and 20,000 ppm formulations were analyzed. Samples (10 g) of the dose formulations were extracted with 25 mL (630 ppm extract) or 100 mL (20,000 ppm extract) acetonitrile:water (90:10) and shaken for 30 minutes. The extracts were then centrifuged for 5 minutes. The 20,000 ppm extract was then separated into 5 mL aliquots and diluted to 23 mL with the acetonitrile:water solution. To remove water from the extracts, 5 mL portions of the diluted 20,000 ppm extract and the undiluted 630 ppm extract were combined with 3 g of anhydrous sodium sulfate and allowed to stand for 15 minutes with periodic shaking. Aliquots (3 mL) of the anhydrous solution were added to 3 mL of derivatizing reagent (reagent-grade acetic anhydride in a solution of hexadecane diluted with pyridine) and then heated in a 50° C water bath for 15 minutes. Portions of the resulting solutions were then analyzed by gas chromatography using a flame ionization detector and 10% SP-2100 on 100/120 mesh Supelcoport and a nitrogen carrier gas at a flow rate of 30 mL/minute and an oven temperature program of 160° C for 20 minutes, then 160° C to 200°C at 10° C/minute with a hold for 10 minutes at 200° C. For the stability analyses, 630 and 20,000 ppm were

prepared, stored up to 21 days in the dark at 5° or −20° C or under animal room conditions, then analyzed by the same gas chromatography method described for the homogeneity analysis. Homogeneity was confirmed; stability of the 630 ppm formulation was confirmed for at least 3 weeks when stored in sealed containers in the dark at −20° C. Based on these observations, the dose formulations were stored in the dark at −20° C for no more than 3 weeks.

Periodic analyses of the dose formulations of 2,2-bis(bromomethyl)-1,3-propanediol were conducted at the study laboratory with gas chromatography using a flame ionization detector and 10% SP-2100 on Supelcoport 100/120 mesh and a nitrogen carrier gas at a flow rate of 30 mL/minute and an isothermal oven temperature of 165° C for 15 minutes, then 165° to 200° C at 10° C per minute and 200° C for 7 minutes. For the 13-week studies, dose formulations were analyzed at the beginning, in the middle, and at the end of the studies (Table I2). During the 2-year studies, formulations were analyzed at least every 10 weeks (Table I3). All the dose formulations analyzed for rats and mice were within 10% of the target concentration during the 13-week studies. During the 2-year rat study, dose formulations were within 10% of the target concentrations 88% (75/85) of the time. The dose formulations found to be outside the acceptable limits were remixed and reanalyzed, and all formulations were within 10% of the target concentration except one (−11%). The 2-year mouse study dose formulations were within 10% of the target concentrations 98% (44/45) of the time. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

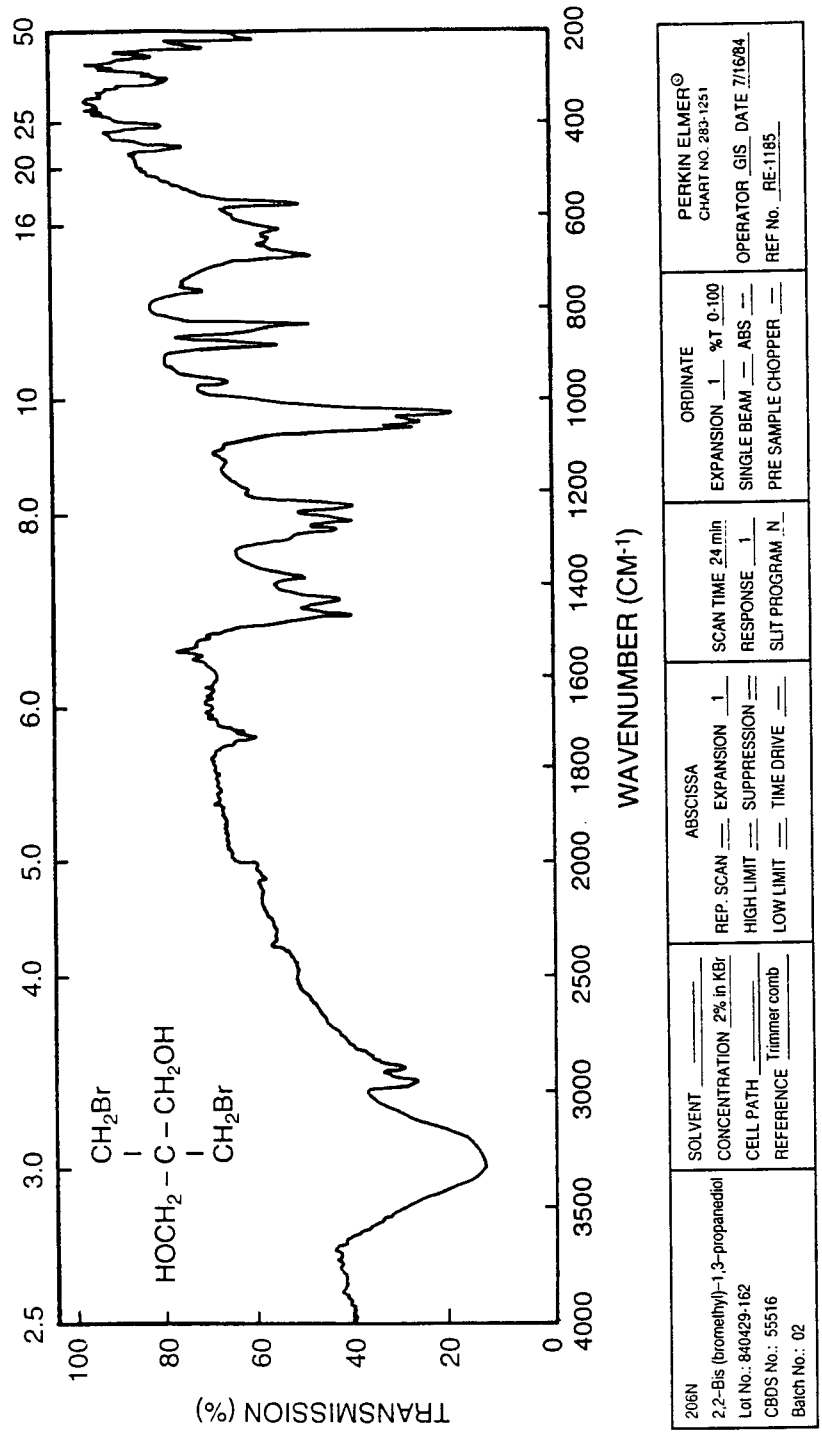


FIGURE I1
Infrared Absorption Spectrum of 2,2-Bis(bromomethyl)-1,3-propanediol

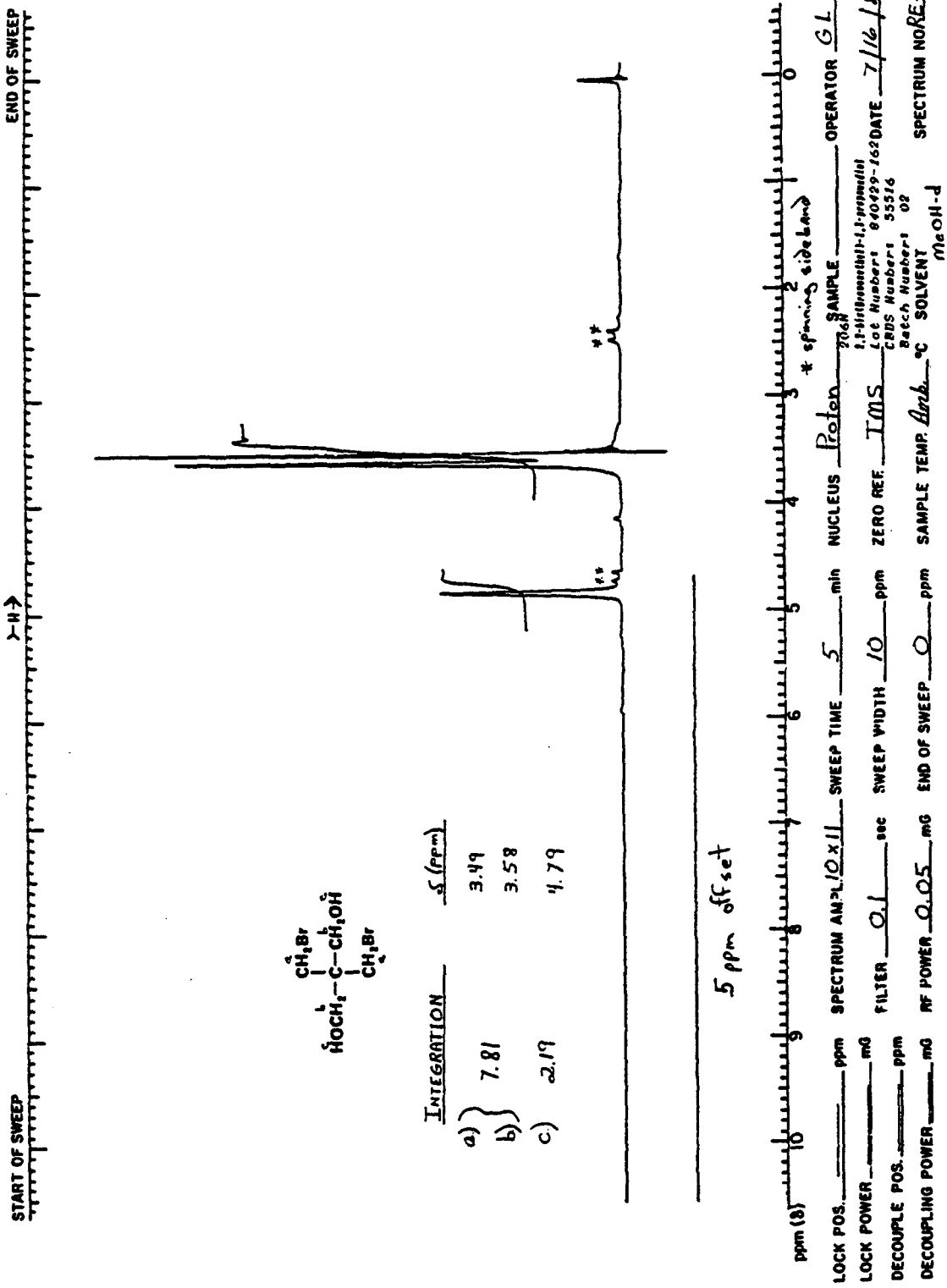
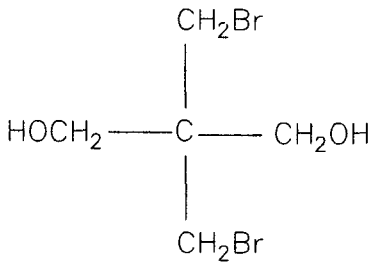
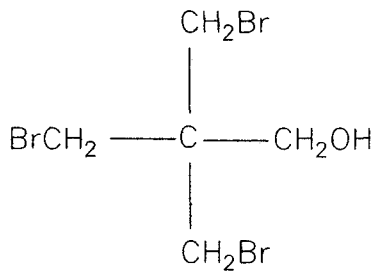


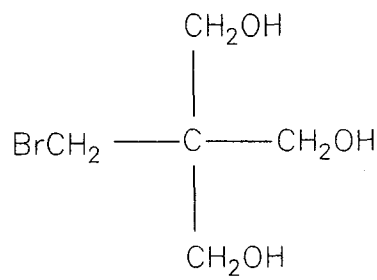
FIGURE I2
Nuclear Magnetic Resonance Spectrum of 2,2-Bis(bromomethyl)-1,3-propanediol



78.6% 2,2-Bis(bromomethyl)-1,3-propanediol
(Dibromoneopentyl Glycol)



6.9% 2,2-Bis(bromomethyl)-1-bromo-3-hydroxypropane
(Tribromoneopentyl Alcohol)



6.6% 2,2-Bis(hydroxymethyl)-1-bromo-3-hydroxypropane
(Monobromoneopentyltriol)

FIGURE I3
Structures and Names of the Parent Compound and Major Impurities

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

13-Week Studies	2-Year Studies
Preparation	
A premix of feed and 2,2-bis(bromomethyl)-1,3-propanediol was prepared by milling mixtures of the chemical and feed in a Udy® Cyclone Sample Mill. The premix was then layered into the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Doses were prepared weekly.	Same as 13-week studies
Chemical Lot Number	
840429-162	840429-162
Maximum Storage Time	
3 weeks	2 weeks
Storage Conditions	
Stored in sealed containers protected from light at −20° C in double plastic bags	Same as 13-week studies
Study Laboratory	
American Biogenics Corporation (Woburn, MA)	Southern Research Institute (Birmingham, AL)
Referee Laboratory	
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
4 February 1986	5 February 1986	20	19.91[b]	−1
		20	19.82[c]	−1
		20	19.55[d]	−2
8 April 1986	9 April 1986	1.25	1.199	−4
		1.25	1.186[e]	−5
		2.5	2.372	−5
		2.5	2.459[e]	−2
		5	4.705	−6
		5	4.902[e]	−2
9 April 1986	11 April 1986	10	9.74	−3
		20	20.26	+1
20 May 1986	21 May 1986	1.25	1.274	+2
		1.25	1.242	−1
		2.5	2.474	−1
		2.5	2.513	+1
		5	4.968	−1
		5	4.917	−2
		10	9.91	−1
		10	9.76	−2
		20	19.57	−2
		20	19.59	−2
28 July 1986	29 July 1986	1.25	1.176	−6
		2.5	2.414	−3
		5	5.018	0
28 July 1986	14 August 1986	10	9.81	−2
		20	19.66	−2
Mice				
8 April 1986	9 April 1986	0.625	0.6652	+6
		0.652	0.6221[e]	−1
		1.25	1.199	−4
		1.25	1.186[e]	−5
		2.5	2.372	−5
		2.5	2.459[e]	−2
		5	4.705	−6
		5	4.902[e]	−2
9 April 1986	11 April 1986	10	9.74	−3

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Mice (continued)				
20 May 1986	21 May 1986	0.625	0.6301	+1
		1.25	1.274	+2
		2.5	2.474	−1
		5	4.968	−1
21 May 1986	22 May 1986	10	9.91	−1
30 June 1986	1 July 1986	0.625	0.6072	−3
		1.25	1.212	−3
		2.5	2.476	−1
		5	4.989	0
1 July 1986	2 July 1986	10	9.83	−2

[a] Results of duplicate analyses. For rats, 20 mg/g = 20,000 ppm. For mice, 0.625 mg/kg = 625 ppm; for rats and mice, 1.25 mg/g = 1,250 ppm; 2.5 mg/g = 2,500 ppm; 5 mg/g = 5,000 ppm; 10 mg/g = 10,000 ppm.
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of single analysis by internal standard method

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
27 February 1989	28 February - 3 March 1989	20	20.4[b]	+2
		20	19.5[c]	−2
		20	20.1[d]	+1
17 March 1989	20-21 March 1989	2.5	2.66	+6
		2.5	2.70	+8
		5	5.50	+10
		5	4.26	−15
		10	10.4	+4
		10	10.1	+1
		20	19.6	−2
		20	21.2	+6
23 March 1989[e]	24 March 1989	5	5.07	+1
18 May 1989	19, 20, and 22 May 1989	2.5	2.35	−6
		2.5	2.42	−3
		5	5.13	+3
		5	5.44	+9
		10	10.2	+2
		10	10.2	+2
		20	20.8	+4
		20	20.3	+2
27 July 1989	27-29 July 1989	2.5	2.48	−1
		2.5	2.52	+1
		5	4.99	0
		5	4.90	−2
		10	10.0	0
		10	10.1	+1
7 September 1989	8-9 September 1989	2.5	2.56	+2
		2.5	2.50	0
		5	5.22	+4
		5	5.23	+5
		10	10.4	+4
		10	14.8	+48
13 September 1989[e]	14 September 1989	10	10.1	+1
2 November 1989	2-4 November 1989	2.5	2.48	−1
		2.5	2.68	+7
		5	5.25	+5
		5	5.18	+4
		10	10.2	+2
		10	10.5	+5

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Rats (continued)				
14 December 1989	14-16 December 1989	2.5	2.15	−14
		2.5	2.20	−12
		5	4.88	−2
		5	4.88	−2
		10	10.3	+3
		10	10.3	+3
18 December 1989[e]	19 December 1989	2.5	2.52	+1
		2.5	2.55	+2
8 February 1990	8-13 February 1990	2.5	2.47	−1
		2.5	2.47	−1
		5	4.92	−2
		5	5.02	0
		10	10.4	+4
		10	9.92	−1
5 April 1990	5-7 April 1990	2.5	2.57	+3
		2.5	2.90	+16
		5	5.62	+12
		5	5.42	+8
		10	9.98	0
		10	10.2	+2
10 April 1990[e]	10 April 1990	2.5	2.40	−4
		5	3.80	−24
11 April 1990[e]	12-13 April 1990	5	4.47	−11
21 June 1990	21-25 June 1990	2.5	2.62	+5
		2.5	2.64	+6
		5	4.74	−5
		5	5.09	+2
		10	10.0	0
		10	10.2	+2
16 August 1990	16-18 August 1990	2.5	2.46	−2
		2.5	2.65	+6
		5	5.11	+2
		5	5.03	+1
		10	10.0	0
		10	10.2	+2
25 October 1990	25, 26, and 29-31 October 1990	2.5	2.45	−2
		2.5	2.38	−5
		5	4.88	−2
		5	4.23	−16
		10	11.3	+13
		10	12.1	+21

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Rats (continued)				
1 November 1990[e]	1-2 November 1990	5	4.90	−2
		10	9.82	−2
		10	9.91	−1
3 January 1991	3-6 January 1991	2.5	2.42	−3
		2.5	2.40	−4
		5	4.92	−2
		5	5.19	+4
		10	10.3	+3
		10	10.1	+1
7 March 1991	7-9 March 1991	2.5	2.52	+1
		2.5	2.42	−3
		5	5.16	+3
		5	5.40	+8
		10	11.1	+11
		10	9.4	−6
12 March 1991[e]	12-13 March 1991	10	10.4	+4
Mice				
27 February 1989	28 February - 3 March 1989	0.312	0.321[b]	+3
		0.312	0.313[c]	0
		0.312	0.311[d]	0
7-8 March 1989	8-9 March 1989	0.312	0.336	+8
		0.312	0.332	+6
		0.625	0.663	+6
		0.625	0.648	+4
		1.25	1.32	+6
		1.25	1.31	+5
18 May 1989	19, 20, and 22 May 1989	0.312	0.324	+4
		0.625	0.610	−2
		1.25	1.20	−4
27 July 1989	27-29 July 1989	0.312	0.321	+3
		0.625	0.599	−4
		1.25	1.24	−1
7 September 1989	8-9 September 1989	0.312	0.332	+6
		0.625	0.626	0
		1.25	1.24	−1
2 November 1989	2-4 November 1989	0.312	0.320	+3
		0.625	0.618	−1
		1.25	1.22	−2

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Mice (continued)				
14 December 1989	14-16 December 1989	0.312	0.334	+7
		0.625	0.612	−2
		1.25	1.24	−1
8 February 1990	8-13 February 1990	0.312	0.327	+5
		0.625	0.630	+1
		1.25	1.22	−2
5 April 1990	5-7 April 1990	0.312	0.311	0
		0.625	0.617	−1
		1.25	1.27	+2
21 June 1990	21-25 June 1990	0.312	0.324	+4
		0.625	0.586	−6
		1.25	1.16	−7
16 August 1990	16-18 August 1990	0.312	0.319	+2
		0.625	0.659	+6
		1.25	1.22	−2
25 October 1990	25, 26, and 29-31 October 1990	0.312	0.322	+3
		0.625	0.654	+5
		1.25	1.24	−1
3 January 1991	3-6 January 1991	0.312	0.312	0
		0.625	0.619	−1
		1.25	1.26	+1
7 March 1991	7-9 March 1991	0.312	0.226	−28
		0.625	0.633	+1
		1.25	1.26	+1
12 March 1991[e]	12-13 March 1991	0.312	0.285	−9

[a] Results of duplicate analyses. For rats, 2.5 mg/g = 2,500 ppm; 5 mg/g = 5,000 ppm; 10 mg/g = 10,000 ppm; 20 mg/g = 20,000 ppm. For mice, 0.312 mg/g = 312 ppm; 0.625 mg/g = 625 ppm; 1.25 mg/g = 1,250 ppm.
[b] Sample selection from top right of twin-shell blender
[c] Sample selection from top left of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of remix

TABLE I4
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g) Study Laboratory[a]	Determined Concentration (mg/g) Referee Laboratory[b]
13-Week Studies (American Biogenics Corp.)			
Rats			
8 April 1986	1.25	1.199	1.20 ± 0.04
Mice			
1 July 1986	10	9.83	9.845 ± 0.143
2-Year Studies (Southern Research Institute)			
Rats			
17 March 1989	10	10.3[c]	10.9 ± 1.06
8 February 1990	2.5	2.47	2.51 ± 0.13
Mice			
8 March 1989	0.625	0.656[c]	0.663 ± 0.02

[a] Results of duplicate analyses. For rats and mice, 0.625 mg/g = 625 ppm; 1.25 mg/g = 1,250 ppm; 2.5 mg/g = 2,500 ppm; 10 mg/g = 10,000 ppm.
[b] Results of triplicate analyses (mean ± standard error)
[c] Average of results from two sets of duplicate analyses

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		2,500 ppm			5,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.6	163	15.2	161	236	14.8	157	471
6	18.2	267	17.4	260	167	16.8	253	332
10	16.5	314	16.5	306	135	16.7	300	279
13	16.7	341	17.1	333	129	16.7	326	256
17	16.5	365	15.9	355	112	16.4	346	238
21	16.8	386	17.6	374	117	16.5	362	227
25	16.0	399	16.1	386	104	15.7	376	209
29	16.8	412	16.5	401	103	15.3	384	199
33	16.3	424	16.4	413	99	16.5	401	205
37	16.0	432	16.2	423	96	15.1	412	183
41	14.5	442	15.2	431	88	15.3	424	180
45	15.8	440	16.0	432	93	16.3	420	194
49	15.9	452	15.9	438	91	16.3	430	189
53	15.7	454	15.6	444	88	15.9	438	182
57	16.5	458	15.9	454	88	15.0	446	169
61	15.8	461	16.0	452	88	16.1	438	184
65	16.1	463	15.6	449	87	15.7	445	176
73	15.5	455	15.2	446	85	14.9	435	171
77	15.1	450	14.7	443	83	15.1	431	175
81	14.4	444	14.9	442	84	13.6	428	159
85	14.2	443	14.4	442	82	12.5	428	146
89	13.2	440	13.8	440	79	11.7	418	140
93	13.5	435	13.2	429	77	12.6	412	152
97	13.8	432	13.6	433	78	12.4	403	154
101	12.6	432	12.6	426	74	13.5	408	166
Mean for weeks								
1-13	16.7	271	16.6	265	167	16.3	259	335
14-52	16.1	417	16.2	406	100	15.9	395	203
53-101	14.7	447	14.6	442	83	14.1	427	165

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.6	163	14.7	152	965	12.6	134	1,881
6	18.2	267	16.2	236	685	14.7	197	1,489
10	16.5	314	16.1	273	590	14.1	222	1,267
13	16.7	341	16.4	298	548	16.0	245	1,308
17	16.5	365	15.3	319	481	15.2	292	1,041
21	16.8	386	16.0	340	471	16.4	323	1,013
25	16.0	399	15.8	355	445	15.3	347	885
29	16.8	412	15.8	367	429	14.7	366	806
33	16.3	424	15.9	377	422	15.5	382	810
37	16.0	432	15.7	388	404	14.9	399	750
41	14.5	442	14.7	396	372	14.6	410	713
45	15.8	440	15.7	395	398	15.9	410	778
49	15.9	452	16.7	401	416	15.6	419	744
53	15.7	454	15.6	414	377	15.3	430	713
57	16.5	458	15.8	418	379	15.0	431	697
61	15.8	461	16.3	415	393	15.6	422	741
65	16.1	463	15.6	414	377	16.3	429	758
73	15.5	455	14.8	406	365	13.3	423	630
77	15.1	450	14.2	416	341	15.2	424	718
81	14.4	444	11.4	407	281	13.3	414	641
85	14.2	443	12.6	402	315	13.1	410	637
89	13.2	440	12.9	394	327	11.8	409	577
93	13.5	435	13.5	388	348	8.9	374	478
97	13.8	432	12.4	384	323	15.2	402	755
101	12.6	432	12.2	369	331			
Mean for weeks								
1-13	16.7	271	15.8	240	697	14.4	200	1,486
14-52	16.1	417	15.7	371	426	15.4	372	838
53-101	14.7	447	14.0	402	347	13.9	415	668

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm		2,500 ppm			5,000 ppm			10,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	11.6	130	11.5	127	226	11.4	126	452	11.5	127	909
6	11.6	168	11.9	165	180	11.8	165	357	11.3	159	707
10	10.8	185	10.8	180	149	10.7	178	301	10.7	172	621
13	10.1	191	10.2	187	136	10.3	186	277	10.0	180	558
17	10.6	201	10.3	198	130	10.2	193	265	9.9	186	532
21	9.9	206	10.4	203	127	10.1	198	254	10.1	192	524
25	9.7	212	10.0	209	120	9.8	203	241	9.6	199	483
29	10.2	220	10.2	214	119	9.6	211	229	9.7	205	475
33	10.2	224	10.5	220	119	10.4	214	244	10.1	209	485
37	9.7	231	9.9	229	108	9.8	221	220	9.9	215	460
41	9.7	238	9.8	234	105	9.7	237	206	9.8	224	439
45	10.6	246	11.2	240	116	10.9	234	233	10.9	228	479
49	10.8	258	11.0	254	108	11.1	247	224	9.4	239	395
53	11.1	268	11.8	265	111	11.0	257	213	11.2	247	454
57	11.7	282	11.5	277	103	11.1	270	206	11.7	259	451
61	11.6	289	12.0	284	106	11.5	275	210	11.4	262	435
65	12.8	299	12.1	293	103	11.5	283	203	11.1	269	414
73	11.8	308	11.9	300	100	11.5	291	197	11.3	277	410
77	11.7	314	12.0	305	98	11.6	295	196	11.7	284	411
81	10.5	313	11.2	308	91	11.0	299	183	10.3	291	356
85	11.0	312	11.3	307	92	10.6	296	179	10.7	286	376
89	10.6	315	10.8	314	86	10.2	305	167	10.0	293	341
93	10.9	319	11.6	318	91	10.8	311	173	10.4	297	351
97	11.4	326	10.2	325	79	11.8	323	183	11.1	301	367
101	10.9	330	11.5	327	88	11.2	322	174	12.2	307	396
Mean for weeks											
1-13	11.0	168	11.1	165	173	11.0	164	347	10.9	159	699
14-52	10.2	226	10.4	222	117	10.2	218	235	9.9	211	475
53-101	11.3	306	11.5	302	96	11.1	294	190	11.1	281	397

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	24.9	4.6	24.9	57	4.4	24.8	111	4.6	24.7	230
6	4.9	28.8	4.9	28.7	53	5.0	28.3	109	4.9	28.2	218
10	4.7	31.8	5.0	32.2	48	4.7	31.4	94	4.8	31.1	193
13	4.6	33.5	4.7	33.7	43	4.7	32.9	90	4.7	32.6	180
17	4.7	34.8	5.0	35.0	45	5.1	34.0	94	4.9	33.8	182
21	4.4	36.9	4.8	37.7	40	4.8	36.7	81	4.8	36.3	164
25	4.3	38.8	4.6	39.6	36	4.4	38.5	72	4.6	37.8	150
29	4.5	40.7	4.6	41.3	35	4.6	40.1	72	4.7	39.7	148
33	4.7	42.2	4.7	43.5	34	4.9	41.7	73	5.0	41.2	153
37	4.8	43.6	4.7	44.4	33	4.9	43.2	70	4.8	42.4	143
41	4.4	44.5	4.7	44.8	32	4.6	44.1	65	4.8	43.3	140
45	4.2	46.4	4.4	46.8	29	4.5	45.9	61	4.6	45.1	127
49	4.4	46.7	4.7	46.9	31	4.5	46.5	61	4.4	45.2	120
53	4.4	47.3	4.7	47.6	31	4.7	46.9	62	4.5	46.1	123
57	4.5	48.2	4.7	49.1	30	4.6	48.5	59	4.8	47.5	125
61	4.7	48.8	4.7	49.4	30	4.7	49.1	60	4.5	48.1	118
65	4.7	49.0	4.9	49.2	31	4.8	49.4	61	4.8	48.0	126
69	4.5	47.6	4.7	48.9	30	4.6	48.5	60	4.4	47.9	116
73	4.3	48.4	4.7	48.7	30	4.6	47.8	60	4.5	47.6	119
77	4.5	48.1	4.7	49.1	30	4.6	48.5	60	4.5	47.7	119
81	4.4	47.3	4.6	47.8	30	4.3	47.1	57	4.4	46.0	120
85	4.7	48.8	4.9	48.7	32	4.8	48.5	61	4.9	46.2	133
90	4.2	49.4	4.5	49.3	29	4.5	47.9	58	4.3	47.2	115
93	4.1	49.7	4.5	49.3	28	4.4	48.6	56	4.4	46.9	117
97	4.5	49.8	4.7	48.9	30	4.5	48.6	58	4.6	46.6	124
101	4.4	48.7	4.5	48.3	29	4.5	47.6	59	4.4	44.6	122
Mean for weeks											
1-13	4.7	29.7	4.8	29.9	50	4.7	29.3	101	4.7	29.2	205
14-52	4.5	41.6	4.7	42.2	35	4.7	41.2	72	4.7	40.5	148
53-101	4.4	48.5	4.7	48.8	30	4.6	48.2	59	4.6	47.0	121

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	20.5	4.5	20.7	68	4.6	20.3	143	4.4	20.2	272
6	4.9	24.3	5.1	24.1	66	5.4	23.7	141	5.3	23.5	279
10	5.1	26.5	5.2	26.9	61	5.3	26.5	124	5.5	26.0	267
13	5.3	28.0	5.0	28.8	54	5.2	28.0	116	5.3	27.5	241
17	4.9	30.1	5.3	30.7	54	5.4	29.9	112	5.4	29.1	233
21	5.0	31.6	5.2	32.6	50	5.4	32.5	104	5.4	30.9	217
25	5.0	34.5	5.1	35.8	44	5.2	35.6	91	5.2	33.7	191
29	4.8	36.2	5.1	37.8	42	4.9	37.5	81	5.3	35.5	185
33	5.3	37.4	5.5	39.4	43	5.5	39.0	88	5.8	37.0	195
37	5.5	39.3	5.6	41.5	42	5.6	41.1	86	6.0	38.9	192
41	4.9	40.7	5.2	43.2	37	5.2	43.0	76	5.5	40.7	168
45	5.1	42.8	4.8	44.8	33	4.9	44.5	69	5.4	43.0	157
49	4.8	44.8	4.9	46.3	33	5.1	45.4	71	4.8	44.0	137
53	5.0	46.0	5.0	48.1	32	5.2	47.2	69	4.9	45.8	135
57	5.0	48.0	5.0	50.3	31	5.0	48.6	65	5.2	47.9	137
61	5.1	49.6	5.1	51.4	31	5.0	50.4	63	5.1	49.6	128
65	5.0	50.2	5.1	52.1	30	5.5	51.7	67	5.6	49.5	142
69	4.5	50.0	5.0	51.6	30	5.2	50.9	64	5.1	49.0	129
73	4.7	50.8	5.1	51.1	31	5.1	51.2	62	5.0	49.3	127
77	4.7	50.9	5.1	51.1	31	4.8	50.5	60	5.2	49.1	133
81	4.7	50.2	5.0	50.0	31	4.7	50.2	59	4.8	49.1	121
85	5.3	52.4	5.3	51.1	33	5.5	51.2	67	6.1	50.3	151
89	4.5	53.6	4.6	52.4	28	4.4	52.0	53	4.9	50.7	120
93	4.4	53.9	4.9	52.6	29	4.6	51.9	55	4.9	49.7	124
97	4.8	54.5	4.9	53.7	29	4.9	51.9	60	5.2	49.4	133
101	4.7	52.4	4.6	52.3	28	4.7	50.8	57	4.9	47.6	128
Mean for weeks											
1-13	4.9	24.8	5.0	25.1	62	5.1	24.6	131	5.1	24.3	265
14-52	5.0	37.5	5.2	39.1	42	5.2	38.7	86	5.4	37.0	186
53-101	4.8	51.0	5.0	51.4	30	5.0	50.6	62	5.1	49.0	131

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

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

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.44 ± 0.83	21.30 — 25.20	25
Crude fat (% by weight)	5.24 ± 0.22	4.80 — 5.80	25
Crude fiber (% by weight)	3.60 ± 0.55	2.60 — 4.80	25
Ash (% by weight)	6.55 ± 0.20	6.12 — 7.10	25
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 — 1.390	10
Cystine	0.306 ± 0.075	0.181 — 0.400	10
Glycine	1.160 ± 0.050	1.060 — 1.220	10
Histidine	0.580 ± 0.024	0.531 — 0.608	10
Isoleucine	0.917 ± 0.034	0.867 — 0.965	10
Leucine	1.972 ± 0.052	1.850 — 2.040	10
Lysine	1.273 ± 0.051	1.200 — 1.370	10
Methionine	0.437 ± 0.115	0.306 — 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 — 1.110	10
Threonine	0.896 ± 0.055	0.824 — 0.985	10
Tryptophan	0.223 ± 0.160	0.107 — 0.671	10
Tyrosine	0.677 ± 0.105	0.564 — 0.794	10
Valine	1.089 ± 0.057	0.962 — 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 — 2.570	9
Linolenic	0.277 ± 0.036	0.210 — 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,664 ± 1,277	4,273 — 9,190	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 — 48.9	9
Thiamine (ppm)	19.76 ± 2.65	15.0 — 28.0	25
Riboflavin (ppm)	7.92 ± 0.93	6.10 — 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 — 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 — 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 — 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 — 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 — 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 — 65.0	10
Choline (ppm)	3,068 ± 314	2,400 — 3,430	9
Minerals			
Calcium (%)	1.22 ± 0.11	0.90 — 1.55	25
Phosphorus (%)	0.95 ± 0.04	0.88 — 1.03	25
Potassium (%)	0.887 ± 0.067	0.772 — 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 — 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 — 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 — 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 — 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 — 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 — 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 — 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 — 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 — 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 — 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 — 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.30 ± 0.16	0.06 — 0.60	25
Cadmium (ppm)	0.08 ± 0.02	0.05 — 0.12	25
Lead (ppm)	0.27 ± 0.18	0.10 — 0.90	25
Mercury (ppm)	0.03 ± 0.02	0.05 — 0.08	25
Selenium (ppm)	0.34 ± 0.08	0.15 — 0.52	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)[c]	15.22 ± 4.43	5.90 — 22.00	25
Nitrite nitrogen (ppm)[c]	0.20 ± 0.14	<0.10 — 0.60	25
BHA (ppm)[d]	1.54 ± 0.88	<1.00 — 4.00	25
BHT (ppm)[d]	1.46 ± 1.25	<1.00 — 7.00	25
Aerobic plate count (CFU/g)	95,068 ± 78,430	4,700 — 380,000	25
Coliform (MPN/g)	28.84 ± 31.01	<3.00 — 93.00	25
Escherichia coli (MPN/g)	3.32 ± 1.21	<3.00 — 9.00	25
Salmonella (MPN/g)	Negative		
Total nitrosoamines (ppb)[e]	7.30 ± 2.45	2.00 — 13.70	25
N-Nitrosodimethylamine (ppb)[e]	5.38 ± 2.06	1.00 — 11.00	25
N-Nitrosopyrrolidine (ppb)[e]	1.92 ± 1.04	1.00 — 4.30	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.27 ± 0.29	0.05 — 1.29	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
13-Week Study	
ELISA	
CARB (cilia-associated respiratory bacillus)	Study termination
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
RCV/SDA	18 months and study termination
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

MICE

13-Week Study

Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	18 months
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
MVM	6 months
Mouse adenoma virus	6 and 18 months, study termination
MHV	6, 12, 18, 21, and 22 months, study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, 18, 21, and 22 months, study termination
Sendai	6, 12, 18, 21, and 22 months, study termination
Immunofluorescence Assay	
EDIM	6 and 12 months, study termination
GDVII	18 months
LCM	18 months and study termination
MVM	12 months
Mouse adenoma virus	12 and 18 months
MHV	18 months
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	18 months and study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/1[a]	None positive
2-Year Studies		
Rats		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
Study termination	2/9	*M. arthritidis*[b]
Mice		
6 Months	0/8	None positive
12 Months	0/10	None positive
18 Months	0/9	None positive
21 Months	2/10	MHV
22 Months	0/10	None positive
Study termination	4/4	MHV
	10/10	MHV
	4/5	MHV

[a] Six samples were received at Microbiological Associates, Inc.; however, on the day they were to be tested, five vials were found to be empty.

[b] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical signs or histopathologic changes of *M. arthritidis* infection in rats with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

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NIH Publication No. 96-3368
May 1996

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	45
Sarcoma, metastatic, mesentery											X															1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma		X																								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Hepatocellular carcinoma, multiple														X											X	2
Hepatocellular adenoma	X			X	X										X		X					X	X		X	13
Hepatocellular adenoma, multiple								X								X			X							3
Histiocytic sarcoma																										1
Sarcoma, metastatic, mesentery											X															1
Mesentery											+				+											6
Sarcoma											X															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, mesentery											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma												X									X	X				3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X												X								2
Parathyroid gland	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma											X										X					5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	4 0 1	4 4 9	4 5 6	4 8 0	4 8 3	4 9 0	5 0 2	5 2 0	5 2 6	5 3 4	5 3 4	5 3 7	5 3 7	5 5 1	5 5 1	5 5 4	5 7 5	5 7 6	5 8 6	6 0 6	6 1 0	6 1 5	6 4 2	6 4 9	6 4 9
Carcass ID Number	4 6 4	4 2 2	4 4 0	4 6 2	4 4 1	4 4 5	4 5 7	4 4 2	4 6 0	4 3 7	4 3 8	4 2 4	4 4 7	4 4 9	4 6 1	4 3 5	4 2 5	4 2 7	4 6 3	4 2 6	4 2 9	4 6 5	4 3 4	4 5 5	4 6 7
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Hemangiosarcoma																									
Polyp stromal																									
Sarcoma stromal																						X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+								+				+		+		+	+						+	
Renal, sarcoma, metastatic, skin															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymph node, mediastinal	+																+							+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	M	+	+	+	+
Sarcoma, metastatic, mesentery																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma			X																						
Carcinoma								X																X	
Carcinoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma				X						X		X			X					X			X	X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X														
Skeletal muscle				+								+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																			+						
Spinal cord																			+						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma		X																								1
Granulosa cell tumor benign			X																							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								2
Hemangiosarcoma										X																1
Polyp stromal														X												1
Sarcoma stromal													X													2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Lymph node															+		+									9
Renal, sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mediastinal																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Thymus	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	42
Sarcoma, metastatic, mesentery											X															1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adenoacanthoma																										1
Carcinoma																										2
Carcinoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									1
Subcutaneous tissue, fibrosarcoma													X													1
Subcutaneous tissue, hemangiosarcoma												X											X			2
Subcutaneous tissue, sarcoma	X				X									X								X				11
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
	0	4	5	8	8	9	0	2	2	3	3	3	3	5	5	5	7	7	8	0	1	1	4	4
	1	9	6	0	3	0	2	0	6	4	4	7	7	1	1	4	5	6	6	6	0	5	2	9	9
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	6	2	4	6	4	4	5	4	6	3	3	2	4	4	6	3	2	2	6	2	2	6	3	5	6
	4	2	0	2	1	5	7	2	0	7	8	4	7	9	1	5	5	7	3	6	9	5	4	5	7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X	X	X									X		X	X
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland																									
Carcinoma, metastatic, mammary gland																		X							
Histiocytic sarcoma																					X				
Sarcoma, metastatic, skin															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+										+	
Harderian gland	+	+				+		+					+	+		+	+	+	+	+		+	+	+	+
Adenoma														X			X		X	X			X	X	X
Carcinoma																	X			X					X
Bilateral, adenoma																						X			
Zymbal's gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol: 1,250 ppm (continued)

Number of Days on Study	6 5 6	6 6 7	6 6 8	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 6 9	6 7 2	6 7 4	6 7 7	7 1 9	7 3 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	4 4 3	4 5 0	4 3 6	4 2 1	4 3 1	4 4 4	4 4 8	4 5 2	4 5 6	4 2 3	4 3 2	4 4 6	4 3 3	4 2 8	4 3 0	4 3 9	4 5 1	4 5 3	4 5 4	4 5 8	4 5 9	4 6 6	4 6 8	4 6 9	4 7 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X		X	X							X	X	X				X		X			X				15
Alveolar/bronchiolar adenoma, multiple															X											2
Alveolar/bronchiolar carcinoma				X									X						X				X			4
Alveolar/bronchiolar carcinoma, multiple														X												1
Carcinoma, metastatic, harderian gland								X																		1
Carcinoma, metastatic, mammary gland																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+		+	+		+										+							7
Harderian gland	+		+	+	+	+	+	+	+		+		+		+	+	+		+		+	+	+		+	33
Adenoma				X	X				X				X			X			X				X			14
Carcinoma	X					X	X	X																		7
Bilateral, adenoma																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																	X			X	X					3

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	2/52 (4%)	6/50 (12%)	8/51 (16%)	15/50 (30%)
Adjusted rate[b]	4.3%	17.7%	23.7%	55.7%
Terminal rate[c]	0/37 (0%)	3/30 (10%)	4/26 (15%)	3/11 (27%)
First incidence (days)	447	669	557	551
Life table test[d]	P<0.001	P=0.105	P=0.030	P<0.001
Logistic regression test[d]	P<0.001	P=0.125	P=0.040	P<0.001
Cochran-Armitage test[d]	P<0.001			
Fisher exact test[d]		P=0.122	P=0.043	P<0.001
Harderian Gland: Carcinoma				
Overall rate	1/52 (2%)	6/50 (12%)	5/51 (10%)	7/50 (14%)
Adjusted rate	2.5%	17.6%	16.1%	25.0%
Terminal rate	0/37 (0%)	4/30 (13%)	3/26 (12%)	0/11 (0%)
First incidence (days)	646	627	669	575
Life table test	P=0.002	P=0.043	P=0.073	P=0.007
Logistic regression test	P=0.095	P=0.052	P=0.098	P=0.033
Cochran-Armitage test	P=0.051			
Fisher exact test		P=0.050	P=0.098	P=0.026
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/52 (6%)	12/50 (24%)	13/51 (25%)	19/50 (38%)
Adjusted rate	6.7%	33.3%	37.5%	64.2%
Terminal rate	0/37 (0%)	7/30 (23%)	7/26 (27%)	3/11 (27%)
First incidence (days)	447	627	557	551
Life table test	P<0.001	P=0.009	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.010	P=0.006	P=0.002
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.009	P=0.006	P<0.001
Liver: Hepatocellular Adenoma				
Overall rate	16/51 (31%)	12/50 (24%)	5/50 (10%)	16/49 (33%)
Adjusted rate	39.4%	36.8%	17.9%	74.1%
Terminal rate	13/37 (35%)	10/30 (33%)	4/26 (15%)	7/11 (64%)
First incidence (days)	569	627	707	480
Life table test	P=0.004	P=0.458N	P=0.042N	P=0.004
Logistic regression test	P=0.181	P=0.305N	P=0.010N	P=0.197
Cochran-Armitage test	P=0.490			
Fisher exact test		P=0.273N	P=0.007N	P=0.531
Liver: Hepatocellular Carcinoma				
Overall rate	5/51 (10%)	8/50 (16%)	5/50 (10%)	3/49 (6%)
Adjusted rate	13.5%	20.2%	17.2%	19.6%
Terminal rate	5/37 (14%)	2/30 (7%)	4/26 (15%)	1/11 (9%)
First incidence (days)	743 (T)	579	557	642
Life table test	P=0.411	P=0.211	P=0.423	P=0.345
Logistic regression test	P=0.314N	P=0.258	P=0.588	P=0.522
Cochran-Armitage test	P=0.202N			
Fisher exact test		P=0.264	P=0.617	P=0.380N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	20/51 (39%)	19/50 (38%)	9/50 (18%)	18/49 (37%)
Adjusted rate	49.5%	48.7%	30.6%	77.1%
Terminal rate	17/37 (46%)	11/30 (37%)	7/26 (27%)	7/11 (64%)
First incidence (days)	569	579	557	480
Life table test	P=0.010	P=0.415	P=0.098N	P=0.003
Logistic regression test	P=0.418	P=0.563N	P=0.019N	P=0.227
Cochran-Armitage test	P=0.335N			
Fisher exact test		P=0.531N	P=0.016N	P=0.480N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/52 (6%)	3/50 (6%)	9/51 (18%)	17/50 (34%)
Adjusted rate	7.7%	8.8%	29.1%	64.2%
Terminal rate	2/37 (5%)	2/30 (7%)	5/26 (19%)	4/11 (36%)
First incidence (days)	640	619	669	534
Life table test	P<0.001	P=0.590	P=0.024	P<0.001
Logistic regression test	P<0.001	P=0.642	P=0.048	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.642	P=0.057	P<0.001
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/52 (4%)	2/50 (4%)	6/51 (12%)	5/50 (10%)
Adjusted rate	5.3%	6.7%	17.6%	33.9%
Terminal rate	1/37 (3%)	2/30 (7%)	3/26 (12%)	2/11 (18%)
First incidence (days)	705	743 (T)	428	669
Life table test	P=0.003	P=0.617	P=0.085	P=0.009
Logistic regression test	P=0.048	P=0.659	P=0.125	P=0.094
Cochran-Armitage test	P=0.102			
Fisher exact test		P=0.676	P=0.128	P=0.202
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/52 (10%)	5/50 (10%)	15/51 (29%)	19/50 (38%)
Adjusted rate	12.7%	15.3%	43.4%	71.9%
Terminal rate	3/37 (8%)	4/30 (13%)	8/26 (31%)	5/11 (45%)
First incidence (days)	640	619	428	534
Life table test	P<0.001	P=0.517	P=0.004	P<0.001
Logistic regression test	P<0.001	P=0.597	P=0.011	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.604	P=0.010	P<0.001
Mammary Gland: Carcinoma				
Overall rate	0/52 (0%)	0/50 (0%)	1/51 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	3.8%	8.7%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	0/11 (0%)
First incidence (days)	—[e]	—	743 (T)	520
Life table test	P=0.006	—	P=0.430	P=0.083
Logistic regression test	P=0.028	—	P=0.430	P=0.163
Cochran-Armitage test	P=0.019			
Fisher exact test		—	P=0.495	P=0.114

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Pancreatic Islets: Adenoma				
Overall rate	1/51 (2%)	3/50 (6%)	2/49 (4%)	2/49 (4%)
Adjusted rate	2.1%	10.0%	6.4%	13.2%
Terminal rate	0/37 (0%)	3/30 (10%)	0/26 (0%)	1/11 (9%)
First incidence (days)	569	743 (T)	707	669
Life table test	P=0.164	P=0.252	P=0.456	P=0.274
Logistic regression test	P=0.370	P=0.295	P=0.477	P=0.490
Cochran-Armitage test	P=0.484			
Fisher exact test		P=0.301	P=0.485	P=0.485
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/50 (8%)	8/48 (17%)	2/48 (4%)	5/46 (11%)
Adjusted rate	10.8%	24.0%	8.0%	21.9%
Terminal rate	4/37 (11%)	5/29 (17%)	2/25 (8%)	1/11 (9%)
First incidence (days)	743 (T)	619	743 (T)	537
Life table test	P=0.126	P=0.098	P=0.528N	P=0.093
Logistic regression test	P=0.493	P=0.133	P=0.528N	P=0.421
Cochran-Armitage test	P=0.535N			
Fisher exact test		P=0.159	P=0.359N	P=0.447
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	8/48 (17%)	3/48 (6%)	5/46 (11%)
Adjusted rate	10.8%	24.0%	12.0%	21.9%
Terminal rate	4/37 (11%)	5/29 (17%)	3/25 (12%)	1/11 (9%)
First incidence (days)	743 (T)	619	743 (T)	537
Life table test	P=0.103	P=0.098	P=0.603	P=0.093
Logistic regression test	P=0.452	P=0.133	P=0.603	P=0.421
Cochran-Armitage test	P=0.553N			
Fisher exact test		P=0.159	P=0.523N	P=0.447
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	0/52 (0%)	1/50 (2%)	4/51 (8%)	11/50 (22%)
Adjusted rate	0.0%	3.1%	11.1%	38.1%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	1/11 (9%)
First incidence (days)	—	696	536	480
Life table test	P<0.001	P=0.466	P=0.053	P<0.001
Logistic regression test	P<0.001	P=0.491	P=0.058	P=0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.490	P=0.057	P<0.001
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/52 (0%)	1/50 (2%)	4/51 (8%)	12/50 (24%)
Adjusted rate	0.0%	3.1%	11.1%	42.8%
Terminal rate	0/37 (0%)	0/30 (0%)	1/26 (4%)	1/11 (9%)
First incidence (days)	—	696	536	480
Life table test	P<0.001	P=0.466	P=0.053	P<0.001
Logistic regression test	P<0.001	P=0.491	P=0.058	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.490	P=0.057	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/52 (0%)	1/50 (2%)	5/51 (10%)	3/50 (6%)
Adjusted rate	0.0%	2.4%	16.6%	24.0%
Terminal rate	0/37 (0%)	0/30 (0%)	3/26 (12%)	2/11 (18%)
First incidence (days)	—	625	639	677
Life table test	P=0.003	P=0.495	P=0.017	P=0.008
Logistic regression test	P=0.022	P=0.504	P=0.029	P=0.028
Cochran-Armitage test	P=0.070			
Fisher exact test		P=0.490	P=0.027	P=0.114
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/51 (6%)	1/50 (2%)	3/51 (6%)	0/50 (0%)
Adjusted rate	8.1%	3.3%	10.6%	0.0%
Terminal rate	3/37 (8%)	1/30 (3%)	2/26 (8%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	709	—
Life table test	P=0.429N	P=0.382N	P=0.509	P=0.396N
Logistic regression test	P=0.355N	P=0.382N	P=0.589	P=0.396N
Cochran-Armitage test	P=0.137N			
Fisher exact test		P=0.316N	P=0.661N	P=0.125N
Uterus: Stromal Polyp				
Overall rate	3/52 (6%)	1/50 (2%)	0/51 (0%)	1/50 (2%)
Adjusted rate	8.1%	3.3%	0.0%	8.3%
Terminal rate	3/37 (8%)	1/30 (3%)	0/26 (0%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	—	733
Life table test	P=0.487N	P=0.382N	P=0.189N	P=0.698
Logistic regression test	P=0.448N	P=0.382N	P=0.189N	P=0.711N
Cochran-Armitage test	P=0.207N			
Fisher exact test		P=0.342N	P=0.125N	P=0.324N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	3/52 (6%)	2/50 (4%)	0/51 (0%)	3/50 (6%)
Adjusted rate	8.1%	6.7%	0.0%	18.3%
Terminal rate	3/37 (8%)	2/30 (7%)	0/26 (0%)	0/11 (0%)
First incidence (days)	743 (T)	743 (T)	—	615
Life table test	P=0.206	P=0.596N	P=0.189N	P=0.194
Logistic regression test	P=0.361	P=0.596N	P=0.189N	P=0.388
Cochran-Armitage test	P=0.584			
Fisher exact test		P=0.519N	P=0.125N	P=0.642
All Organs: Hemangiosarcoma				
Overall rate	0/52 (0%)	0/50 (0%)	0/51 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	20.9%
Terminal rate	0/37 (0%)	0/30 (0%)	0/26 (0%)	1/11 (9%)
First incidence (days)	—	—	—	672
Life table test	P<0.001	—	—	P=0.013
Logistic regression test	P=0.005	—	—	P=0.055
Cochran-Armitage test	P=0.011			
Fisher exact test		—	—	P=0.114

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/52 (2%)	2/50 (4%)	0/51 (0%)	5/50 (10%)
Adjusted rate	2.7%	5.6%	0.0%	27.0%
Terminal rate	1/37 (3%)	0/30 (0%)	0/26 (0%)	1/11 (9%)
First incidence (days)	743 (T)	635	—	649
Life table test	P=0.003	P=0.453	P=0.570N	P=0.008
Logistic regression test	P=0.024	P=0.484	P=0.570N	P=0.039
Cochran-Armitage test	P=0.041			
Fisher exact test		P=0.485	P=0.505N	P=0.094
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	5/52 (10%)	10/50 (20%)	9/51 (18%)	4/50 (8%)
Adjusted rate	12.5%	25.5%	27.6%	36.4%
Terminal rate	4/37 (11%)	5/30 (17%)	5/26 (19%)	4/11 (36%)
First incidence (days)	285	386	543	743 (T)
Life table test	P=0.193	P=0.089	P=0.092	P=0.165
Logistic regression test	P=0.334N	P=0.121	P=0.183	P=0.607
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.115	P=0.184	P=0.525N
All Organs: Histiocytic Sarcoma				
Overall rate	1/52 (2%)	4/50 (8%)	2/51 (4%)	1/50 (2%)
Adjusted rate	2.7%	11.6%	7.3%	3.3%
Terminal rate	1/37 (3%)	2/30 (7%)	1/26 (4%)	0/11 (0%)
First incidence (days)	743 (T)	579	726	610
Life table test	P=0.440	P=0.140	P=0.387	P=0.579
Logistic regression test	P=0.517N	P=0.165	P=0.442	P=0.739
Cochran-Armitage test	P=0.415N			
Fisher exact test		P=0.169	P=0.493	P=0.743
All Organs: Benign Neoplasms				
Overall rate	29/52 (56%)	29/50 (58%)	29/51 (57%)	34/50 (68%)
Adjusted rate	63.7%	75.9%	75.4%	93.9%
Terminal rate	21/37 (57%)	21/30 (70%)	17/26 (65%)	9/11 (82%)
First incidence (days)	285	619	557	480
Life table test	P<0.001	P=0.246	P=0.146	P<0.001
Logistic regression test	P=0.020	P=0.478	P=0.536	P=0.058
Cochran-Armitage test	P=0.119			
Fisher exact test		P=0.489	P=0.535	P=0.143
All Organs: Malignant Neoplasms				
Overall rate	17/52 (33%)	33/50 (66%)	31/51 (61%)	36/50 (72%)
Adjusted rate	40.9%	68.5%	74.0%	91.7%
Terminal rate	13/37 (35%)	15/30 (50%)	16/26 (62%)	8/11 (73%)
First incidence (days)	285	386	397	456
Life table test	P<0.001	P=0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P=0.004	P<0.001
Cochran-Armitage test	P<0.001			
Fisher exact test		P<0.001	P=0.004	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/52 (71%)	43/50 (86%)	43/51 (84%)	42/50 (84%)
Adjusted rate	76.8%	89.5%	93.3%	97.6%
Terminal rate	26/37 (70%)	25/30 (83%)	23/26 (88%)	10/11 (91%)
First incidence (days)	285	386	397	456
Life table test	P<0.001	P=0.043	P=0.013	P<0.001
Logistic regression test	P=0.059	P=0.055	P=0.086	P=0.042
Cochran-Armitage test	P=0.114			
Fisher exact test		P=0.056	P=0.085	P=0.094

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pancreatic islets, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Harderian Gland Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carconoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	3/50	0/50	3/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	3/50	0/50	3/50
Ethylene Glycol	2/50	0/50	2/50
Nitrofurantoin	1/50	1/50	2/50
o-Nitroanisole	0/50	1/50	1/50
p-Nitrobenzoic Acid	3/50	0/50	3/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	5/1,470 (3.5%)	8/1,470 (0.5%)	59/1,470 (4.0%)
Standard deviation	3.1%	0.9%	3.1%
Range	0%-10%	0%-2%	0%-10%

[a] Data as of 31 March 1993

TABLE D4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carconoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	1/50	0/50	1/50
C.I. Pigment Red 23	1/50	0/50	1/50
C.I. Pigment Red 3	3/50	1/50	4/50
Ethylene Glycol	0/50	1/50	1/50
Nitrofurantoin	2/50	1/50	3/50
o-Nitroanisole	4/50	2/50	6/50
p-Nitrobenzoic Acid	3/50	0/50	3/50
Polysorbate 80	3/50	0/50	3/50
Rhodamine 6G	3/50	1/50	4/50
Roxarsone	1/50	2/50	3/50
Overall Historical Incidence			
Total	89/1,469 (5.6%)	30/1,469 (2.0%)	110/1,469 (7.5%)
Standard deviation	4.8%	2.2%	5.0%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 31 March 1993

TABLE D4c
Historical Incidence of Subcutaneous Tissue Skin Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Sarcoma	Fibrosarcoma or Sarcoma
Historical Incidence at Southern Research Institute		
Benzyl Acetate	0/50	0/50
C.I. Pigment Red 23	0/50	0/50
C.I. Pigment Red 3	1/50	3/50
Ethylene Glycol	1/50	1/50
Nitrofurantoin	0/50	0/50
o-Nitroanisole	0/50	0/50
p-Nitrobenzoic Acid	1/50	1/50
Polysorbate 80	0/50	4/50
Rhodamine 6G	0/50	0/50
Roxarsone	0/50	0/50
Overall Historical Incidence		
Total	3/1,470 (0.2%)	21/1,470 (1.4%)
Standard deviation	0.6%	2.2%
Range	0%-2%	0%-8%

[a] Data as of 31 March 1993

TABLE D4d
Historical Incidence of Forestomach Squamous Cell Papilloma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Benzyl Acetate	0/50
C.I. Pigment Red 23	0/50
C.I. Pigment Red 3	0/50
Ethylene Glycol	0/50
Nitrofurantoin	1/50
o-Nitroanisole	3/50
p-Nitrobenzoic Acid	1/50
Polysorbate 80	0/50
Rhodamine 6G	1/50
Roxarsone	0/50
Overall Historical Incidence	
Total	31/1,470 (2.1%)
Standard deviation	2.9%
Range	0%-14%

[a] Data as of 31 March 1993

TABLE D4e
Historical Incidence of Mammary Gland Adenoacanthoma and Carcinoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls	
	Adenoacanthoma	Carcinoma
Historical Incidence at Southern Research Institute		
Benzyl Acetate	0/50	0/50
C.I. Pigment Red 23	0/50	1/50
C.I. Pigment Red 3	0/50	0/50
Ethylene Glycol	0/50	1/50
Nitrofurantoin	0/50	5/50
o-Nitroanisole	0/50	0/50
p-Nitrobenzoic Acid	0/50	0/50
Polysorbate 80	0/50	0/50
Rhodamine 6G	0/50	0/50
Roxarsone	0/50	2/50
Overall Historical Incidence		
Total	0/1,470 (0.0%)	22/1,470 (1.5%)
Standard deviation		2.8%
Range		0%-10%

[a] Data as of 31 March 1993

TABLE D4f
Historical Incidence of Hemangioma and Hemangiosarcoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Heamngiosarcoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	2/50	0/50	2/50
C.I. Pigment Red 23	0/50	0/50	0/50
C.I. Pigment Red 3	2/50	2/50	3/50
Ethylene Glycol	0/50	0/50	0/50
Nitrofurantoin	1/50	2/50	3/50
o-Nitroanisole	2/50	1/50	3/50
p-Nitrobenzoic Acid	0/50	4/50	4/50
Polysorbate 80	1/50	0/50	1/50
Rhodamine 6G	1/50	2/50	2/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	21/1,470 (1.4%)	42/1,470 (2.9%)	60/1470 (4.1%)
Standard deviation	2.0%	2.5%	2.7%
Range	0%-8%	0%-8%	0%-8%

[a] Data as of 31 March 1993

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	8	10	9	10
Early deaths				
Moribund	9	14	14	29
Natural deaths	6	6	11	10
Survivors				
Terminal sacrifice	37	30	26	11
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Esophagus	(8)	(10)	(9)	(10)
Mucosa, hyperplasia				1 (10%)
Liver	(8)	(10)	(9)	(10)
Basophilic focus		1 (10%)		
Eosinophilic focus		1 (10%)		1 (10%)
Inflammation, subacute	2 (25%)	1 (10%)		1 (10%)
Mesentery		(1)	(1)	(2)
Inflammation, chronic			1 (100%)	
Fat, necrosis		1 (100%)		2 (100%)
Pancreas	(8)	(10)	(9)	(10)
Atrophy			1 (11%)	
Focal cellular change		1 (10%)		
Salivary glands	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid		1 (10%)	1 (11%)	1 (10%)
Stomach, forestomach	(8)	(10)	(9)	(10)
Ulcer			2 (22%)	3 (30%)
Mucosa, hyperplasia	1 (13%)		3 (33%)	3 (30%)
Endocrine System				
Adrenal cortex	(8)	(10)	(9)	(10)
Accessory adrenal cortical nodule				2 (20%)
Islets, pancreatic	(8)	(10)	(9)	(10)
Hyperplasia		1 (10%)		
Parathyroid gland	(8)	(9)	(9)	(9)
Cyst			1 (11%)	
Ectopic tissue	1 (13%)			1 (11%)
Pituitary gland	(8)	(10)	(9)	(10)
Pars distalis, hyperplasia, focal	1 (13%)			
Thyroid gland	(8)	(10)	(9)	(9)
Degeneration, cystic		1 (10%)	1 (11%)	
Follicle, cyst		1 (10%)		
Follicular cell, hyperplasia				1 (11%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(8)	(10)	(9)	(10)
Ectasia	7 (88%)	9 (90%)	8 (89%)	10 (100%)
Inflammation, chronic	1 (13%)			
Pigmentation			2 (22%)	
Ovary	(8)	(10)	(9)	(9)
Angiectasis			1 (11%)	1 (11%)
Cyst	1 (13%)	1 (10%)		1 (11%)
Uterus	(8)	(10)	(9)	(10)
Hydrometra		1 (10%)	1 (11%)	1 (10%)
Hyperplasia, cystic	7 (88%)	10 (100%)	9 (100%)	10 (100%)
Inflammation, suppurative	2 (25%)	1 (10%)	1 (11%)	1 (10%)
Metaplasia, squamous				1 (10%)
Hematopoietic System				
Bone marrow	(8)	(10)	(9)	(10)
Hypercellularity				1 (10%)
Lymph node, mandibular	(8)	(10)	(9)	(10)
Hemorrhage			1 (11%)	
Hyperplasia, lymphoid		1 (10%)		
Lymph node, mesenteric	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid	1 (13%)	1 (10%)		
Spleen	(8)	(10)	(9)	(10)
Hematopoietic cell proliferation			1 (11%)	2 (20%)
Pigmentation, hemosiderin				1 (10%)
Lymphoid follicle, hyperplasia				1 (10%)
Integumentary System				
Skin	(7)	(10)	(9)	(10)
Inflammation, subacute				1 (10%)
Musculoskeletal System				
Bone	(8)	(10)	(9)	(10)
Hyperostosis	1 (13%)			1 (10%)
Respiratory System				
Lung	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid			1 (11%)	
Infiltration cellular, histiocyte	1 (13%)			
Thrombosis			1 (11%)	
Alveolar epithelium, hyperplasia	1 (13%)			
Nose	(8)	(10)	(9)	(10)
Exudate	1 (13%)		1 (11%)	
Special Senses System				
Harderian gland	(4)	(5)	(4)	(7)
Hyperplasia			1 (25%)	1 (14%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(8)	(10)	(9)	(10)
Casts protein	2 (25%)	5 (50%)	3 (33%)	4 (40%)
Cyst	1 (13%)		1 (11%)	1 (10%)
Hyperplasia, lymphoid		2 (20%)	2 (22%)	
Renal tubule, regeneration		1 (10%)		1 (10%)
Transitional epithelium, hyperplasia		1 (10%)		
Urinary bladder	(8)	(10)	(9)	(10)
Hyperplasia, lymphoid		1 (10%)	1 (11%)	
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Nervous System				
2-Year Study				
Alimentary System				
Gallbladder	(49)	(47)	(47)	(45)
Dilatation			2 (4%)	1 (2%)
Intestine large, cecum	(52)	(50)	(49)	(50)
Edema	3 (6%)	1 (2%)	4 (8%)	4 (8%)
Intestine small, duodenum	(51)	(50)	(47)	(49)
Ulcer	1 (2%)			
Intestine small, jejunum	(49)	(49)	(49)	(47)
Peyer's patch, hyperplasia	1 (2%)			
Intestine small, ileum	(51)	(50)	(47)	(47)
Amyloid deposition		1 (2%)		
Liver	(51)	(50)	(50)	(49)
Basophilic focus	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Clear cell focus		1 (2%)		
Cyst			1 (2%)	
Degeneration, fatty	1 (2%)		1 (2%)	3 (6%)
Developmental malformation	1 (2%)			1 (2%)
Eosinophilic focus	4 (8%)	1 (2%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	9 (18%)	6 (12%)	4 (8%)	15 (31%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, subacute	5 (10%)	2 (4%)	2 (4%)	1 (2%)
Mixed cell focus	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Centrilobular, necrosis		1 (2%)	2 (4%)	2 (4%)
Kupffer cell, hyperplasia	6 (12%)	4 (8%)	7 (14%)	12 (24%)
Kupffer cell, pigmentation	2 (4%)		1 (2%)	1 (2%)
Lobules, necrosis	4 (8%)	7 (14%)	6 (12%)	6 (12%)
Mesentery	(4)	(6)	(7)	(6)
Inflammation, chronic			1 (14%)	
Fat, necrosis	4 (100%)	5 (83%)	4 (57%)	5 (83%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(51)	(50)	(49)	(48)
Atrophy	1 (2%)	3 (6%)	2 (4%)	5 (10%)
Cyst	1 (2%)	2 (4%)	3 (6%)	5 (10%)
Focal cellular change				4 (8%)
Hyperplasia, lymphoid		2 (4%)		2 (4%)
Acinar cell, cytoplasmic alteration	4 (8%)	3 (6%)	2 (4%)	2 (4%)
Salivary glands	(52)	(50)	(51)	(50)
Hyperplasia, lymphoid	4 (8%)	3 (6%)	5 (10%)	4 (8%)
Stomach, forestomach	(51)	(50)	(51)	(49)
Diverticulum		1 (2%)	1 (2%)	
Inflammation, suppurative			1 (2%)	1 (2%)
Ulcer	5 (10%)	2 (4%)	5 (10%)	3 (6%)
Mucosa, hyperkeratosis				1 (2%)
Mucosa, hyperplasia	9 (18%)	5 (10%)	13 (25%)	6 (12%)
Stomach, glandular	(51)	(50)	(49)	(49)
Ectopic tissue	1 (2%)			
Edema	1 (2%)		1 (2%)	2 (4%)
Erosion	1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Inflammation, subacute	3 (6%)	1 (2%)	1 (2%)	
Mineralization			1 (2%)	1 (2%)
Ulcer				1 (2%)
Mucosa, hyperplasia	1 (2%)	1 (2%)	2 (4%)	
Cardiovascular System				
Blood vessel	(1)			
Inflammation, subacute	1 (100%)			
Heart	(52)	(50)	(51)	(50)
Inflammation, chronic			1 (2%)	1 (2%)
Mineralization			1 (2%)	1 (2%)
Thrombosis		1 (2%)	1 (2%)	1 (2%)
Myocardium, necrosis			1 (2%)	
Endocrine System				
Adrenal cortex	(51)	(50)	(51)	(49)
Accessory adrenal cortical nodule	5 (10%)	6 (12%)	6 (12%)	4 (8%)
Angiectasis		1 (2%)		
Cyst		2 (4%)		
Degeneration, fatty		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal				1 (2%)
Hypertrophy, focal	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Capsule, hyperplasia	1 (2%)	1 (2%)		
Adrenal medulla	(51)	(50)	(51)	(49)
Atrophy	1 (2%)			
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Islets, pancreatic	(51)	(50)	(49)	(49)
Hyperplasia	2 (4%)	1 (2%)		3 (6%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Parathyroid gland	(44)	(45)	(49)	(47)
Cyst	2 (5%)	4 (9%)	2 (4%)	
Pituitary gland	(50)	(48)	(48)	(46)
Pars distalis, angiectasis	3 (6%)	2 (4%)	5 (10%)	1 (2%)
Pars distalis, cyst	1 (2%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	8 (16%)	4 (8%)	5 (10%)	8 (17%)
Thyroid gland	(51)	(50)	(51)	(50)
Degeneration, cystic	12 (24%)	6 (12%)	13 (25%)	14 (28%)
Ectopic thymus			1 (2%)	
Follicle, cyst	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Follicular cell, hyperplasia	13 (25%)	15 (30%)	9 (18%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(52)	(48)	(51)	(50)
Ectasia	2 (4%)		2 (4%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)	
Ovary	(51)	(49)	(51)	(48)
Angiectasis	9 (18%)	5 (10%)	17 (33%)	11 (23%)
Cyst	10 (20%)	12 (24%)	11 (22%)	16 (33%)
Inflammation, suppurative	8 (16%)	2 (4%)	4 (8%)	6 (13%)
Uterus	(52)	(50)	(51)	(50)
Angiectasis	2 (4%)	6 (12%)	16 (31%)	17 (34%)
Hydrometra	10 (19%)	5 (10%)	7 (14%)	4 (8%)
Hyperplasia, cystic	46 (88%)	41 (82%)	43 (84%)	45 (90%)
Inflammation, granulomatous			1 (2%)	1 (2%)
Inflammation, suppurative	9 (17%)	2 (4%)	5 (10%)	2 (4%)
Metaplasia, squamous	4 (8%)	3 (6%)		
Hematopoietic System				
Bone marrow	(52)	(50)	(51)	(50)
Hypercellularity	13 (25%)	15 (30%)	15 (29%)	25 (50%)
Myelofibrosis	7 (13%)	5 (10%)	6 (12%)	7 (14%)
Necrosis	1 (2%)			
Lymph node	(9)	(12)	(6)	(9)
Bronchial, hyperplasia, lymphoid	1 (11%)			
Iliac, hematopoietic cell proliferation	1 (11%)		1 (17%)	1 (11%)
Iliac, hyperplasia, lymphoid	6 (67%)	1 (8%)		3 (33%)
Inguinal, hyperplasia, lymphoid		1 (8%)		
Mediastinal, hyperplasia, lymphoid	2 (22%)		1 (17%)	3 (33%)
Mediastinal, inflammation, suppurative				1 (11%)
Pancreatic, hematopoietic cell proliferation				1 (11%)
Pancreatic, hyperplasia, lymphoid				1 (11%)
Pancreatic, necrosis		1 (8%)		
Renal, hyperplasia, lymphoid	6 (67%)	2 (17%)		5 (56%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(46)	(50)	(46)
Atrophy	1 (2%)			
Hematopoietic cell proliferation	1 (2%)	1 (2%)		2 (4%)
Hemorrhage				2 (4%)
Hyperplasia, lymphoid	5 (10%)	6 (13%)	8 (16%)	11 (24%)
Pigmentation	6 (13%)	5 (11%)		7 (15%)
Lymph node, mesenteric	(49)	(48)	(46)	(48)
Angiectasis	1 (2%)	1 (2%)	2 (4%)	
Atrophy	1 (2%)			
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Hemorrhage	4 (8%)	4 (8%)	1 (2%)	4 (8%)
Hyperplasia, lymphoid	5 (10%)	3 (6%)	4 (9%)	9 (19%)
Pigmentation				1 (2%)
Spleen	(51)	(50)	(50)	(50)
Hematopoietic cell proliferation	20 (39%)	25 (50%)	25 (50%)	39 (78%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)	
Pigmentation, hemosiderin	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Lymphoid follicle, atrophy	1 (2%)			
Lymphoid follicle, hyperplasia	8 (16%)	3 (6%)	6 (12%)	4 (8%)
Red pulp, atrophy	1 (2%)			
Thymus	(46)	(47)	(46)	(42)
Atrophy	2 (4%)	3 (6%)	4 (9%)	4 (10%)
Ectopic parathyroid gland	1 (2%)			
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Integumentary System				
Mammary gland	(52)	(50)	(50)	(49)
Hyperplasia, cystic	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, lobular	1 (2%)	2 (4%)	1 (2%)	
Skin	(52)	(50)	(51)	(50)
Acanthosis		1 (2%)		
Edema			1 (2%)	1 (2%)
Inflammation, subacute		1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(52)	(50)	(51)	(50)
Hyperostosis	1 (2%)		3 (6%)	2 (4%)
Nervous System				
Brain	(52)	(50)	(51)	(50)
Compression		4 (8%)	2 (4%)	
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, chronic			2 (4%)	
Necrosis			1 (2%)	
Peripheral nerve	(1)	(1)	(1)	(1)
Atrophy	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	312 ppm	625 ppm	1,250 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(52)	(50)	(51)	(50)
Congestion		1 (2%)	1 (2%)	
Foreign body		1 (2%)		1 (2%)
Hemorrhage	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, lymphoid	3 (6%)	5 (10%)	6 (12%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)	5 (10%)	5 (10%)	5 (10%)
Inflammation, subacute	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Mineralization			1 (2%)	
Thrombosis	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	3 (6%)	8 (16%)	15 (30%)
Nose	(52)	(50)	(51)	(50)
Exudate	2 (4%)		1 (2%)	
Special Senses System				
Eye		(2)	(3)	(7)
Cataract		2 (100%)	1 (33%)	2 (29%)
Inflammation, chronic		1 (50%)		5 (71%)
Phthisis bulbi			2 (67%)	1 (14%)
Harderian gland	(18)	(27)	(27)	(33)
Hyperplasia	1 (6%)	1 (4%)	2 (7%)	
Urinary System				
Kidney	(51)	(50)	(51)	(49)
Casts protein	17 (33%)	17 (34%)	13 (25%)	4 (8%)
Cyst	1 (2%)		1 (2%)	
Glomerulosclerosis	1 (2%)	1 (2%)		
Hydronephrosis				1 (2%)
Hyperplasia, lymphoid	9 (18%)	9 (18%)	5 (10%)	4 (8%)
Metaplasia, osseous	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		2 (4%)	1 (2%)
Renal tubule, atrophy	1 (2%)			
Renal tubule, cytoplasmic alteration	1 (2%)	1 (2%)	2 (4%)	
Renal tubule, dilatation	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Renal tubule, necrosis			2 (4%)	1 (2%)
Renal tubule, pigmentation	1 (2%)		1 (2%)	1 (2%)
Renal tubule, regeneration	7 (14%)	10 (20%)	11 (22%)	6 (12%)
Urinary bladder	(51)	(50)	(50)	(50)
Edema	1 (2%)		2 (4%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, subacute			2 (4%)	1 (2%)
Mucosa, hyperplasia	1 (2%)		2 (4%)	1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986) and Zeiger *et al.* (1992). 2,2-Bis(bromomethyl)-1,3-propanediol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of 2,2-bis(bromomethyl)-1,3-propanediol. The high dose was limited by toxicity in the second study. Because toxicity was not a limiting factor in the first study, 10,000 μg/plate was selected as the high dose. All positive assays were repeated under the conditions which elicited the positive response.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 2,2-Bis(bromomethyl)-1,3-propanediol was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of 2,2-bis(bromomethyl)-1,3-propanediol; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26.3 hours with 2,2-bis(bromomethyl)-1,3-propanediol in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26.3 hours, the medium containing 2,2-bis(bromomethyl)-1,3-propanediol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 2,2-bis(bromomethyl)-1,3-propanediol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 2,2-bis(bromomethyl)-1,3-propanediol, and incubation proceeded for an additional 25.5 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Generally, fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in the test without S9, incubation time was

lengthened at the 167 and 500 μg/kg dose levels to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with 2,2-bis(bromomethyl)-1,3-propanediol for 18.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 2,2-bis(bromomethyl)-1,3-propanediol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test. Because cell cycle delay was anticipated in the test conducted without S9, the incubation period was extended approximately 10 to 12 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. Generally, 100 first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose led to an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

Mouse Bone Marrow Micronucleus Test Protocols

Two bone marrow studies were performed. The first employed a 3-dose gavage protocol, with 2,2-bis(bromomethyl)-1,3-propanediol administered at 24-hour intervals followed by bone marrow sampling 24 hours after the third dosing. The second study used a single intraperitoneal injection followed by bone marrow sampling 48 hours after dosing. In the first study, male $B6C3F_1$ mice were administered 2,2-bis(bromomethyl)-1,3-propanediol in corn oil by gavage three times at 24-hour intervals. Solvent control animals were administered corn oil alone, and the positive control mice received injections of 12.5 mg dimethylbenzanthracene per kg body weight. In the second study, 2,2-bis(bromomethyl)-1,3-propanediol was administered to male and female $B6C3F_1$ mice by a single intraperitoneal injection. The solvent control mice were again administered corn oil and the positive control mice were administered urethane (200 mg/kg). In both studies, smears of the bone marrow cells obtained from the femurs were prepared, air-dried, fixed, and stained. In the gavage study, 2,000 polychromatic erythrocytes (PCEs)

were scored for frequency of micronucleated cells in each of 5 animals per dose group. In the injection study, 3 or 4 animals were available for micronucleus analysis in each dose group, and 1,000 PCEs were scored per animal. The results were tabulated as the mean of the pooled results from all animals within a treatment group, plus or minus the standard error of the mean. For the three-treatment gavage study, the frequency of micronucleated cells among PCEs was analyzed by a statistical software package (ILS, 1990) which employed a one-tailed trend test across dose groups and a *t*-test for pairwise comparisons of each dose group to the concurrent control. Data from the single injection micronucleus test were analyzed by the Cochran-Armitage trend test and pairwise comparisons of dose groups to the corresponding negative controls were made using a *t*-test.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 13-week toxicity study. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were sent to the USDA Western Regional Research Center in Albany, CA, where they were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630 or 1,000× magnification using a semi-automated image analysis system to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in as many as 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm UV illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using a Student's *t*-test.

RESULTS

2,2-Bis(bromomethyl)-1,3-propanediol was shown to be mutagenic *in vitro* and *in vivo*, but the conditions required to observe the positive responses were highly specific, and 2,2-bis(bromomethyl)-1,3-propanediol was not active in all assays. In the two *Salmonella* assays reported here (Table E1), 2,2-bis(bromomethyl)-1,3-propanediol gave a positive response only in the second assay (Zeiger *et al.*, 1992), which used a different concentration of S9 than the first assay (Mortelmans *et al.*, 1986). Metabolic activation, specifically in the form of 30% Aroclor 1254-induced male Syrian hamster liver S9, was required to obtain the mutagenic response; 10% hamster S9 was ineffective, as was 10% or 30% S9 derived from livers of pretreated rats. No other *Salmonella* strain/activation combination was responsive to the effects of 2,2-bis(bromomethyl)-1,3-propanediol.

In cytogenetic tests with CHO cells (Galloway *et al.*, 1987), 2,2-bis(bromomethyl)-1,3-propanediol did not induce SCEs, with or without S9 (Table E2), but a dose-related increase in Abs was observed in CHO cells treated in the presence of induced rat liver S9 (Table E3). Both tests were conducted up to doses which induced marked cytotoxicity; cell confluence in the SCE test was reduced 75% at the top dose tested with S9 (1,200 μg/mL). A majority of the breaks which were observed in the aberration assay were located in the heterochromatic region of the long arm of the X chromosome. The reason for this preferential breakage site is not known. Also, the type of damage pattern seen with 2,2-bis(bromomethyl)-

1,3-propanediol (induction of chromosomal aberrations but not sister chromatid exchanges) is unusual. Most chemicals which induce Abs also induce SCEs (Galloway *et al.*, 1987).

2,2-Bis(bromomethyl)-1,3-propanediol was also shown to be genotoxic *in vivo*. Significant increases in micronucleated normochromatic erythrocytes were observed in peripheral blood samples obtained from male and female mice exposed for 13 weeks to 2,2-bis(bromomethyl)-1,3-propanediol in feed (Table E6). These increases were observed in the two highest dose groups of male mice (5,000 and 10,000 ppm) and the three highest dose groups of female mice (2,500 to 10,000 ppm).

In the first of two mouse bone marrow micronucleus tests performed to confirm the positive results seen in the 13-week feed study, inconsistent results were obtained between two trials which used the same dose range of 100 to 400 mg/kg 2,2-bis(bromomethyl)-1,3-propanediol, administered by gavage three times at 24-hour intervals (Table E4). Results of the first trial were negative; however, in the second trial, 2,2-bis(bromomethyl)-1,3-propanediol produced a clear, dose-related increase in micronucleated PCEs. Because the positive response was not reproduced, the results were concluded to be equivocal.

In an attempt to clarify the results obtained in the first bone marrow micronucleus test, a second investigation was performed using both male and female mice. 2,2-Bis(bromomethyl)-1,3-propanediol was administered as a single intraperitoneal injection (150 to 600 mg/kg) and bone marrow samples were taken 48 hours after dosing. The results of this experiment, shown in Table E5, provide evidence of the ability of 2,2-bis(bromomethyl)-1,3-propanediol to induce micronuclei in bone marrow cells of female mice. Although male mice in all three dose groups showed a two-fold increase in the frequency of micronucleated PCEs, the trend test was not significant due to the similarity in the responses, and pairwise analyses were also insignificant. The response in female mice was somewhat stronger (2.5-fold increase over background, at the highest dose) and was directly related to increasing doses of 2,2-bis(bromomethyl)-1,3-propanediol. These results were consistent with the stronger response observed in female mice in the 13-week feed study (Table E4).

In conclusion, 2,2-bis(bromomethyl)-1,3-propanediol was genotoxic *in vitro* and *in vivo*, inducing gene mutations in *Salmonella* strain TA100, chromosomal aberrations in Chinese hamster ovary cells, and micronuclei in erythrocytes of male and female mice. The *in vitro* responses required S9.

TABLE E1
Mutagenicity of 2,2-Bis(bromomethyl)-1,3-propanediol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] −S9 Trial 1	−S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Case Western Reserve University							
TA100	0	69 ± 3.8	83 ± 3.5	77 ± 4.2	94 ± 9.0	81 ± 3.2	76 ± 4.6
	10		64 ± 6.0				
	33	76 ± 1.9	59 ± 6.0				
	100	64 ± 5.3	56 ± 3.5	88 ± 6.2	105 ± 11.3	93 ± 7.3	85 ± 4.8
	333	55 ± 5.0	61 ± 4.0	105 ± 7.5	93 ± 4.0	85 ± 7.3	76 ± 4.8
	1,000	toxic	56 ± 2.5	112 ± 7.2	107 ± 9.5	93 ± 1.2	79 ± 6.0
	3,333	toxic		126 ± 0.0	106 ± 8.5	82 ± 6.9	85 ± 7.0
	10,000			toxic	110 ± 10.0	toxic	71 ± 8.4
Trial summary		Negative	Negative	Weakly Positive	Negative	Negative	Negative
Positive control[c]		625 ± 45.2	429 ± 44.2	1,468 ± 2.9	1,171 ± 157.7	1,362 ± 92.4	1,044 ± 44.5
TA1535	0	6 ± 0.9	7 ± 0.7	6 ± 0.6	10 ± 0.9	8 ± 0.3	6 ± 2.0
	10						
	33	4 ± 0.9	6 ± 0.6				
	100	5 ± 1.9	9 ± 1.5	10 ± 1.7	10 ± 1.3	10 ± 2.1	10 ± 2.0
	333	2 ± 1.0	6 ± 0.6	17 ± 2.4	14 ± 1.9	11 ± 2.2	10 ± 1.2
	1,000	3 ± 1.2	10 ± 1.8	14 ± 3.2	10 ± 4.5	10 ± 0.3	10 ± 0.3
	3,333	2 ± 0.7	toxic	16 ± 3.0	16 ± 1.8	12 ± 1.7	10 ± 0.9
	10,000			12 ± 1.2	14 ± 1.9	10 ± 1.8	11 ± 0.7
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		471 ± 110.0	488 ± 98.5	128 ± 3.9	113 ± 15.5	280 ± 31.9	71 ± 11.6
TA1537	0	2 ± 0.9	6 ± 0.6	6 ± 1.9	10 ± 1.5	7 ± 0.9	10 ± 1.5
	33	1 ± 0.3	4 ± 1.2				
	100	1 ± 0.6	8 ± 0.9	5 ± 0.9	7 ± 1.2	5 ± 1.5	6 ± 1.2
	333	0 ± 0.3	7 ± 1.8	3 ± 0.3	7 ± 1.0	6 ± 2.1	10 ± 1.5
	1,000	0 ± 0.0	3 ± 2.0	6 ± 1.5	10 ± 2.1	2 ± 0.9	9 ± 0.3
	3,333	1 ± 0.3	3 ± 3.0	2 ± 1.0	9 ± 1.2	2 ± 0.9	7 ± 0.6
	10,000			2 ± 0.9	toxic	2 ± 0.6	7 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		432 ± 12.9	55 ± 6.8	74 ± 3.5	52 ± 7.0	58 ± 3.0	71 ± 15.8
TA98	0	21 ± 2.2	18 ± 4.0	11 ± 0.9	21 ± 3.2	10 ± 0.6	23 ± 1.7
	10		11 ± 1.5				
	33	9 ± 1.5	12 ± 1.2				
	100	12 ± 2.4	11 ± 1.2	15 ± 1.8	14 ± 4.4	12 ± 1.2	20 ± 0.3
	333	7 ± 1.3	12 ± 1.5	13 ± 1.8	19 ± 4.6	12 ± 1.0	20 ± 1.2
	1,000	toxic	8 ± 0.3	10 ± 2.1	22 ± 1.2	13 ± 3.4	19 ± 2.3
	3,333	toxic		14 ± 0.6	23 ± 1.9	13 ± 1.2	20 ± 3.8
	10,000			3 ± 0.9	19 ± 3.5	8 ± 1.2	21 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		129 ± 18.0	462 ± 34.7	1,076 ± 45.0	854 ± 74.9	481 ± 83.0	568 ± 8.4

TABLE E1
Mutagenicity of 2,2-Bis(bromomethyl)-1,3-propanediol in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate −S9 Trial 1	−S9 Trial 2	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% rat S9
Study performed at SRI, Inc.						
TA100	0	159 ± 3.5	161 ± 11.1	151 ± 4.7	160 ± 10.2	170 ± 9.0
	10		149 ± 11.8			
	33		164 ± 13.5			
	100	152 ± 7.0	150 ± 10.4	156 ± 8.1	172 ± 11.5	154 ± 10.1
	333	161 ± 12.7	154 ± 5.4	233 ± 15.6	225 ± 17.5	154 ± 3.5
	1,000	154 ± 5.8	188 ± 4.2	335 ± 11.9	364 ± 21.4	157 ± 5.8
	1,666				414 ± 32.8	
	3,333	0 ± 0.0[d]		533 ± 14.9	502 ± 32.4	171 ± 5.5
	6,666	toxic		477 ± 39.8		173 ± 8.1
Trial summary		Negative	Negative	Positive	Positive	Negative
Positive control		503 ± 5.2	1,132 ± 62.5	812 ± 50.9	845 ± 18.8	529 ± 7.9

Strain	Dose (μg/plate)	Revertants/plate −S9 Trial 1	−S9 Trial 2	+30% S9 hamster	+30% S9 rat
TA98	0	28 ± 2.2	32 ± 6.1	35 ± 2.7	43 ± 3.5
	10		32 ± 4.7		
	33		41 ± 5.5		
	100	30 ± 3.5	32 ± 0.3	36 ± 3.5	46 ± 4.5
	333	35 ± 2.9	29 ± 0.6	34 ± 2.9	44 ± 6.1
	1,000	27 ± 3.3	44 ± 4.7	30 ± 1.8	50 ± 5.8
	3,333	23 ± 3.4[d]		39 ± 3.8	31 ± 3.8
	6,666	toxic		29 ± 3.5	40 ± 1.5
Trial summary		Negative	Negative	Negative	Negative
Positive control		677 ± 20.6	464 ± 26.2	770 ± 11.3	168 ± 3.5

[a] The detailed protocol and these data for the study performed at Case Western Reserve University are presented in Mortelmans *et al.* (1986); protocol and data for the study performed at SRI, Inc. are presented in Zeiger *et al.* (1992). 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

[d] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 2,2-Bis(bromomethyl)-1,3-propanediol[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
−S9								
Summary: Negative								
Dimethylsulfoxide		50	1,038	496	0.47	9.9	26.3	
Mitomycin-C	0.005	25	519	692	1.33	27.7	26.3	179.03
2,2-Bis(bromomethyl)-1,3-propanediol	16.7	50	1,041	485	0.46	9.7	26.3	−2.50
	50	50	1,042	498	0.47	10.0	26.3	0.02
	167	50	1,050	545	0.51	10.9	33.5[c]	8.62
	500	0					33.5[c]	
					P=0.077[d]			
+S9								
Summary: Equivocal								
Dimethylsulfoxide		50	1,050	496	0.47	9.9	25.5	
Cyclophosphamide	1.5	25	523	840	1.60	33.6	25.5	240.00
2,2-Bis(bromomethyl)-1,3-propanediol	800	50	1,048	556	0.53	11.1	25.5	12.31
	1,000	50	1,047	590	0.56	11.8	25.5	19.29
	1,200[e]	50	1,046	574	0.54	11.5	25.5	16.17
					P=0.004			

[a] Study performed at Litton Bionetics, Inc. A detailed description of the protocol and these data are presented in Galloway *et al.* (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells.
[c] Due to chemical-induced cell cycle delay, incubation time was extended to provide sufficient cells for scoring.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[e] Marked toxicity noted at this dose level

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2,2-Bis(bromomethyl)-1,3-propanediol[a]

−S9					+S9				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 20.5 hours[b]					Harvest time: 10.5 hours				
Summary: Negative					Summary: Positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	2	0.02	2.0		100	5	0.05	5.0
Mitomycin-C					Cyclophosphamide				
0.062	50	10	0.20	16.0	50	50	19	0.38	28.0
2,2-Bis(bromomethyl)-1,3-propanediol					2,2-Bis(bromomethyl)-1,3-propanediol				
400	100	1	0.01	1.0	600	100	8	0.08	4.0
500	100	2	0.02	2.0	800	100	24	0.24	22.0*
600	100	0	0.00	0.0	1,000	100	17	0.17	16.0*
700	0				1,200	0			
				P=0.833[c]					P≤0.001

* Positive ($P<0.05$)

[a] Study performed at Litton Bionetics, Inc. The detailed protocol and these data are presented in Galloway *et al.* (1987). Abs = aberrations.

[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.

[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE E4
Frequency of Micronuclei in Bone Marrow Cells of Male Mice Treated with 2,2-Bis(bromomethyl)-1,3-propanediol by Gavage[a]

Dose (mg/kg)[b]	Micronucleated Cells/1,000 PCEs[c]
Trial 1 - Negative	
Dimethylbenzanthracene[d]	
12.5	4.6 ± 1.1
2,2-Bis(bromomethyl)-1,3-propanediol	
0	1.4 ± 0.6
100	0.7 ± 0.4
200	2.5 ± 0.5
300	2.0 ± 0.7
400[e]	1.2 ± 1.2
	P=0.220[f]
Trial 2 - Positive	
Dimethylbenzanthracene	
12.5	7.8 ± 1.3
2,2-Bis(bromomethyl)-1,3-propanediol	
0	1.5 ± 0.5
100	2.3 ± 0.3
200	2.6 ± 0.7
400	4.8 ± 1.2*
	P=0.000

* Significantly different (P<0.008) from control
[a] Study performed at Environmental Health Research and Testing, Inc. Two thousand PCEs scored per animal.
[b] 0 mg/kg dose is corn oil control.
[c] Data presented as mean ± standard error; PCE = polychromatic erythrocyte
[d] Positive control
[e] Only 2 mice survived in this dose group.
[f] Trend test

TABLE E5
Frequency of Micronuclei in Bone Marrow Cells of Mice Treated with 2,2-Bis(bromomethyl)-1,3-propanediol by Intraperitoneal Injection[a]

Dose (mg/kg)[b]	Number of Mice	Micronucleated Cells/1,000 PCEs[c]
Male		
Urethane[d]		
200	3	16.4 ± 2.2
2,2-Bis(bromomethyl)-1,3-propanediol		
0	4	1.5 ± 0.3
150	4	3.2 ± 0.8*
300	4	3.0 ± 0.7*
600	3	3.0 ± 1.0*
		P=0.150[e]
Female		
Urethane		
200	4	12.1 ± 0.9
2,2-Bis(bromomethyl)-1,3-propanediol		
0	4	2.0 ± 0.4
150	4	2.7 ± 1.1
300	3	3.6 ± 0.9*
600	4	5.2 ± 0.5*
		P=0.003

* Significantly different ($P<0.008$) from control
[a] One thousand PCEs scored per animal. 2,2-Bis(bromomethyl)-1,3-propanediol was administered by intraperitoneal injection, and bone marrow was sampled 48 hours later.
[b] 0 mg/kg dose is corn oil control.
[c] Data presented as mean ± standard error; PCE = polychromatic erythrocyte
[d] Positive control
[e] Trend test

TABLE E6
Frequency of Micronucleated Normochromatic Erythrocytes in Mouse Peripheral Blood Following Treatment with 2,2-Bis(bromomethyl)-1,3-propanediol in Feed for 13 Weeks[a]

Dose (ppm)	Micronucleated NCEs/1,000 Cells[b]	Number of Mice
Male		
0	2.36 ± 0.17	10
625	2.28 ± 0.29	8
1,250	2.55 ± 0.18	10
2,500	2.98 ± 0.21	10
5,000	3.80 ± 0.19[c]	10
10,000	9.30 ± 1.26[c]	7
	P<0.001[d]	
Female		
0	1.46 ± 0.26	9
625	1.86 ± 0.30	9
1,250	1.86 ± 0.22	9
2,500	2.72 ± 0.32[c]	9
5,000	4.26 ± 0.47[c]	9
10,000	11.81 ± 0.54[c]	9
	P<0.001	

[a] Ten thousand NCEs scored per animal. The detailed protocol and these data are presented in MacGregor *et al.* (1990). 0 ppm is the control.
[b] Data presented as mean ± standard error; NCE = normochromatic erythrocyte
[c] Significant response by pairwise comparison to control
[d] Trend test

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Core Study						
Male						
n	10	10	10	10	10	9
Necropsy body wt	334 ± 6	336 ± 5	317 ± 4	308 ± 10*	299 ± 8**	255 ± 7**
Brain						
Absolute	2.037 ± 0.019	2.010 ± 0.023	2.028 ± 0.022	2.018 ± 0.023	1.981 ± 0.012	1.948 ± 0.016**
Relative	6.13 ± 0.12	6.00 ± 0.11	6.41 ± 0.06	6.60 ± 0.16*	6.66 ± 0.15**	7.69 ± 0.16**
Heart						
Absolute	1.214 ± 0.035	1.225 ± 0.043	1.196 ± 0.025	1.202 ± 0.037	1.182 ± 0.053	1.152 ± 0.048
Relative	3.65 ± 0.12	3.65 ± 0.13	3.78 ± 0.06	3.93 ± 0.17	3.95 ± 0.13	4.50 ± 0.21**
R. Kidney						
Absolute	1.224 ± 0.027	1.251 ± 0.029	1.234 ± 0.014	1.227 ± 0.038	1.240 ± 0.024	1.173 ± 0.028
Relative	3.68 ± 0.09	3.73 ± 0.06	3.90 ± 0.06	3.99 ± 0.09*	4.16 ± 0.11**	4.62 ± 0.12**
Liver						
Absolute	12.534 ± 0.167	12.106 ± 0.375	12.071 ± 0.258	12.206 ± 0.524	13.200 ± 0.231	12.322 ± 0.300
Relative	37.64 ± 0.48	36.03 ± 0.69	38.18 ± 0.90	39.61 ± 0.98	44.32 ± 0.99**	48.49 ± 1.08**
Lungs						
Absolute	1.660 ± 0.082	1.856 ± 0.059	1.663 ± 0.088	1.523 ± 0.038	1.630 ± 0.042	1.376 ± 0.048**
Relative	4.97 ± 0.21	5.55 ± 0.22	5.25 ± 0.26	4.98 ± 0.16	5.49 ± 0.22	5.45 ± 0.26
Spleen						
Absolute	0.736 ± 0.015	0.745 ± 0.015	0.701 ± 0.014	0.689 ± 0.019	0.718 ± 0.013	0.620 ± 0.012**
Relative	2.21 ± 0.04	2.22 ± 0.04	2.21 ± 0.03	2.25 ± 0.05	2.41 ± 0.06**	2.43 ± 0.06**
R. Testis						
Absolute	1.492 ± 0.027	1.458 ± 0.038[b]	1.503 ± 0.019[b]	1.443 ± 0.035	1.411 ± 0.038	1.360 ± 0.036**
Relative	4.49 ± 0.12	4.36 ± 0.09[b]	4.76 ± 0.07[b]	4.71 ± 0.14	4.74 ± 0.13	5.31 ± 0.15**
Thymus						
Absolute	0.319 ± 0.010	0.335 ± 0.013	0.317 ± 0.024	0.286 ± 0.014	0.270 ± 0.019	0.251 ± 0.019**
Relative	0.96 ± 0.02	1.00 ± 0.04	1.00 ± 0.07	0.94 ± 0.05	0.90 ± 0.06	0.96 ± 0.08
Female						
n	10	10	10	10	10	10
Necropsy body wt	200 ± 6	192 ± 3	189 ± 2	184 ± 3**	174 ± 6**	163 ± 2**
Brain						
Absolute	1.912 ± 0.022	1.899 ± 0.013	1.838 ± 0.018*	1.856 ± 0.018	1.888 ± 0.017	1.861 ± 0.015
Relative	9.65 ± 0.29	9.90 ± 0.12	9.73 ± 0.10	10.09 ± 0.12	11.01 ± 0.46**	11.43 ± 0.19**
Heart						
Absolute	0.836 ± 0.018	0.796 ± 0.029	0.781 ± 0.018	0.788 ± 0.023	0.793 ± 0.023	0.748 ± 0.029
Relative	4.20 ± 0.10	4.14 ± 0.14	4.13 ± 0.10	4.29 ± 0.14	4.62 ± 0.22	4.59 ± 0.17
R. Kidney						
Absolute	0.772 ± 0.022	0.757 ± 0.017	0.728 ± 0.019	0.749 ± 0.022	0.728 ± 0.014	0.710 ± 0.017
Relative	3.88 ± 0.10	3.94 ± 0.07	3.85 ± 0.09	4.06 ± 0.09	4.25 ± 0.20*	4.35 ± 0.07**
Liver						
Absolute	6.891 ± 0.209	6.567 ± 0.147	6.470 ± 0.204	6.679 ± 0.135	6.253 ± 0.120**	6.317 ± 0.044**
Relative	34.58 ± 0.80	34.21 ± 0.66	34.20 ± 0.92	36.25 ± 0.40	36.39 ± 1.41	38.81 ± 0.66**
Lungs						
Absolute	1.142 ± 0.039	1.159 ± 0.050	1.027 ± 0.018	1.213 ± 0.037	1.060 ± 0.022	1.075 ± 0.037
Relative	5.75 ± 0.21	6.03 ± 0.22	5.44 ± 0.10	6.60 ± 0.23	6.18 ± 0.29	6.60 ± 0.24*
Spleen						
Absolute	0.519 ± 0.013	0.516 ± 0.013	0.520 ± 0.006	0.524 ± 0.010	0.517 ± 0.007	0.509 ± 0.007
Relative	2.62 ± 0.10	2.69 ± 0.06	2.75 ± 0.03	2.85 ± 0.06*	3.01 ± 0.12**	3.13 ± 0.07**
Thymus						
Absolute	0.279 ± 0.009	0.275 ± 0.018	0.267 ± 0.016	0.259 ± 0.019	0.248 ± 0.012	0.239 ± 0.009
Relative	1.40 ± 0.06	1.43 ± 0.09	1.41 ± 0.09	1.40 ± 0.08	1.45 ± 0.10	1.47 ± 0.06

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study						
Male						
n	9	8	9	7	10	10
Necropsy body wt	323 ± 5	327 ± 5	320 ± 3	326 ± 4	302 ± 8**	249 ± 3**
Brain						
Absolute	1.976 ± 0.023	1.994 ± 0.021	1.978 ± 0.036	2.011 ± 0.037	1.976 ± 0.024	1.941 ± 0.024
Relative	6.13 ± 0.05	6.11 ± 0.13	6.18 ± 0.11	6.17 ± 0.09	6.59 ± 0.22*	7.80 ± 0.12**
Heart						
Absolute	1.113 ± 0.034	1.201 ± 0.059	1.171 ± 0.033	1.139 ± 0.039	1.068 ± 0.029	0.985 ± 0.024*
Relative	3.45 ± 0.09	3.69 ± 0.22	3.66 ± 0.09	3.49 ± 0.09	3.56 ± 0.13	3.96 ± 0.11*
R. Kidney						
Absolute	1.353 ± 0.114	1.359 ± 0.032	1.360 ± 0.108	1.355 ± 0.046	1.291 ± 0.034	1.247 ± 0.017
Relative	4.20 ± 0.36	4.16 ± 0.08	4.26 ± 0.36	4.15 ± 0.10	4.29 ± 0.13	5.01 ± 0.07*
Liver						
Absolute	13.691 ± 0.625	15.016 ± 0.646	14.283 ± 0.667	15.543 ± 0.634	15.860 ± 0.638	13.315 ± 0.459
Relative	42.30 ± 1.37	45.85 ± 1.60	44.58 ± 1.98	47.68 ± 1.70	52.81 ± 2.39**	53.46 ± 1.69**
Lung						
Absolute	2.201 ± 0.300	1.959 ± 0.169[c]	1.681 ± 0.083*	1.755 ± 0.070*	1.581 ± 0.060**	1.442 ± 0.034**
Relative	6.83 ± 0.94	6.00 ± 0.50[c]	5.25 ± 0.26	5.39 ± 0.21	5.26 ± 0.20	5.79 ± 0.08
Spleen						
Absolute	0.668 ± 0.024	0.693 ± 0.017	0.699 ± 0.011	0.738 ± 0.016*	0.687 ± 0.014	0.590 ± 0.014**
Relative	2.07 ± 0.06	2.12 ± 0.04	2.18 ± 0.03	2.27 ± 0.05*	2.29 ± 0.09**	2.37 ± 0.03**
R. Testis						
Absolute	1.471 ± 0.020	1.449 ± 0.018	1.484 ± 0.017	1.470 ± 0.026	1.429 ± 0.018	1.405 ± 0.035
Relative	4.57 ± 0.09	4.44 ± 0.07	4.64 ± 0.06	4.51 ± 0.07	4.76 ± 0.12	5.64 ± 0.14**
Thymus						
Absolute	0.304 ± 0.023	0.328 ± 0.025	0.291 ± 0.032	0.280 ± 0.017	0.313 ± 0.023	0.261 ± 0.017
Relative	0.95 ± 0.07	1.00 ± 0.08	0.91 ± 0.10	0.86 ± 0.05	1.04 ± 0.07	1.05 ± 0.06
Female						
n	9	10	9	10	9	10
Necropsy body wt	205 ± 2	204 ± 3	199 ± 2	194 ± 3**	193 ± 3**	170 ± 2**
Brain						
Absolute	1.852 ± 0.023	1.858 ± 0.020	1.876 ± 0.010	1.845 ± 0.024	1.876 ± 0.028	1.808 ± 0.025
Relative	9.05 ± 0.08	9.14 ± 0.14	9.44 ± 0.09	9.50 ± 0.11*	9.73 ± 0.13**	10.64 ± 0.20**
Heart						
Absolute	0.788 ± 0.022	0.745 ± 0.021	0.786 ± 0.024	0.783 ± 0.029	0.766 ± 0.030	0.692 ± 0.021*
Relative	3.85 ± 0.10	3.67 ± 0.11	3.95 ± 0.13	4.04 ± 0.15	3.97 ± 0.14	4.07 ± 0.14
R. Kidney						
Absolute	0.874 ± 0.019	0.850 ± 0.013	0.867 ± 0.016	0.813 ± 0.013*	0.850 ± 0.015	0.816 ± 0.014*
Relative	4.27 ± 0.08	4.18 ± 0.08	4.36 ± 0.06	4.18 ± 0.05	4.41 ± 0.04	4.79 ± 0.06**
Liver						
Absolute	8.255 ± 0.328	8.357 ± 0.329	8.053 ± 0.223	7.813 ± 0.160	8.054 ± 0.225	7.506 ± 0.201
Relative	40.31 ± 1.40	41.09 ± 1.61	40.49 ± 1.14	40.29 ± 0.99	41.79 ± 1.24	44.18 ± 1.39
Lung						
Absolute	1.348 ± 0.023	1.335 ± 0.043	1.367 ± 0.055	1.250 ± 0.068	1.165 ± 0.035*	1.211 ± 0.036*
Relative	6.59 ± 0.14	6.55 ± 0.14	6.87 ± 0.27	6.44 ± 0.37	6.04 ± 0.15	7.12 ± 0.19
Spleen						
Absolute	0.534 ± 0.011	0.534 ± 0.014	0.545 ± 0.010	0.541 ± 0.011	0.527 ± 0.011	0.486 ± 0.012**
Relative	2.61 ± 0.03	2.62 ± 0.05	2.74 ± 0.04	2.79 ± 0.06	2.74 ± 0.06	2.86 ± 0.07**
Thymus						
Absolute	0.250 ± 0.008	0.291 ± 0.016	0.246 ± 0.012	0.280 ± 0.022	0.290 ± 0.022	0.236 ± 0.015
Relative	1.22 ± 0.04	1.43 ± 0.08	1.24 ± 0.06	1.43 ± 0.11	1.50 ± 0.10	1.39 ± 0.10

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=7

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Rats at the 3-Month Interim Evaluation in the 2-Year Stop-Exposure Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	20,000 ppm
n	10	10
Necropsy body wt	344 ± 5	248 ± 6**
R. Kidney		
Absolute	1.231 ± 0.018	1.125 ± 0.026**
Relative	3.59 ± 0.05	4.55 ± 0.07**
Liver		
Absolute	13.762 ± 0.251	11.777 ± 0.287**
Relative	40.08 ± 0.70	47.56 ± 0.27**

** Significantly different ($P \leq 0.01$) from the control group by Williams' test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	9	7	9	5
Necropsy body wt	456 ± 7	453 ± 14	434 ± 9	407 ± 14**
R. Kidney				
Absolute	1.630 ± 0.032	1.603 ± 0.073	1.599 ± 0.041	1.808 ± 0.154
Relative	3.58 ± 0.08	3.54 ± 0.12	3.69 ± 0.09	4.49 ± 0.50**
Liver				
Absolute	15.861 ± 0.165	16.123 ± 0.590	16.604 ± 0.668	15.248 ± 0.603
Relative	34.86 ± 0.59	35.62 ± 1.06	38.24 ± 1.09*	37.42 ± 0.63*
Female				
n	10	9	7	8
Necropsy body wt	297 ± 5	276 ± 6	279 ± 7	281 ± 8
R. Kidney				
Absolute	0.949 ± 0.020	0.924 ± 0.032	0.931 ± 0.025	0.980 ± 0.031
Relative	3.20 ± 0.04	3.35 ± 0.10	3.34 ± 0.05	3.49 ± 0.05**
Liver				
Absolute	8.535 ± 0.190	8.446 ± 0.173	8.624 ± 0.082	9.213 ± 0.366
Relative	28.76 ± 0.33	30.63 ± 0.43**	30.97 ± 0.71**	32.77 ± 0.59**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
n	10	8	10	10	10	7
Necropsy body wt	27.8 ± 1.6	28.0 ± 1.2	27.5 ± 1.0	25.4 ± 0.4	21.6 ± 0.4**	17.4 ± 0.4**
Brain						
Absolute	0.493 ± 0.007	0.465 ± 0.009*	0.465 ± 0.009*	0.486 ± 0.005	0.467 ± 0.004*	0.467 ± 0.008
Relative	18.47 ± 1.50	16.82 ± 0.80	17.14 ± 0.72	19.20 ± 0.36	21.63 ± 0.43**	26.82 ± 0.36**
Heart						
Absolute	0.171 ± 0.005	0.163 ± 0.010	0.170 ± 0.008	0.172 ± 0.009	0.146 ± 0.007*	0.132 ± 0.006**
Relative	6.51 ± 0.75	5.87 ± 0.42	6.23 ± 0.26	6.78 ± 0.35	6.76 ± 0.28	7.58 ± 0.32
R. Kidney						
Absolute	0.284 ± 0.005	0.251 ± 0.004*	0.261 ± 0.006*	0.257 ± 0.007*	0.227 ± 0.007**	0.199 ± 0.016**
Relative	10.63 ± 0.82	9.07 ± 0.35	9.60 ± 0.42	10.15 ± 0.26	10.47 ± 0.23	11.43 ± 0.88
Liver						
Absolute	1.410 ± 0.035	1.405 ± 0.051	1.374 ± 0.037	1.397 ± 0.032	1.114 ± 0.052**	0.948 ± 0.049**
Relative	52.87 ± 4.54	50.36 ± 0.97	50.56 ± 2.26	55.05 ± 1.09	51.27 ± 1.71	54.34 ± 2.60
Lungs						
Absolute	0.179 ± 0.007	0.176 ± 0.005	0.175 ± 0.005	0.194 ± 0.013	0.163 ± 0.005	0.163 ± 0.011
Relative	6.84 ± 0.88	6.35 ± 0.29	6.40 ± 0.19	7.62 ± 0.46	7.56 ± 0.20	9.38 ± 0.65**
Spleen						
Absolute	0.063 ± 0.001	0.059 ± 0.003	0.060 ± 0.003	0.058 ± 0.003	0.041 ± 0.002**	0.040 ± 0.007**
Relative	2.35 ± 0.16	2.11 ± 0.09	2.20 ± 0.14	2.26 ± 0.08	1.88 ± 0.07	2.27 ± 0.38
R. Testis						
Absolute	0.122 ± 0.003	0.120 ± 0.002	0.129 ± 0.004[b]	0.122 ± 0.004	0.114 ± 0.002	0.102 ± 0.005**
Relative	4.59 ± 0.42	4.32 ± 0.16	4.97 ± 0.31[b]	4.82 ± 0.17	5.31 ± 0.15	5.84 ± 0.19**
Thymus						
Absolute	0.039 ± 0.003	0.036 ± 0.003	0.050 ± 0.004	0.039 ± 0.003	0.026 ± 0.003**	0.020 ± 0.004**
Relative	1.49 ± 0.21	1.32 ± 0.15	1.83 ± 0.17	1.51 ± 0.11	1.17 ± 0.13	1.16 ± 0.25

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female						
n	9	9	9	9	9	9
Necropsy body wt	25.8 ± 1.1	25.2 ± 0.9	23.7 ± 1.0	23.9 ± 0.7	18.5 ± 0.3**	16.0 ± 0.6**
Brain						
Absolute	0.488 ± 0.004	0.494 ± 0.002	0.493 ± 0.007	0.496 ± 0.007	0.478 ± 0.004	0.457 ± 0.006**
Relative	19.17 ± 0.83	19.82 ± 0.67	21.04 ± 0.78	20.88 ± 0.64	25.88 ± 0.32**	28.85 ± 1.15**
Heart						
Absolute	0.143 ± 0.005	0.154 ± 0.005	0.149 ± 0.006	0.147 ± 0.005	0.119 ± 0.001**	0.106 ± 0.003**
Relative	5.62 ± 0.29	6.20 ± 0.35	6.31 ± 0.22	6.18 ± 0.24	6.45 ± 0.10*	6.70 ± 0.30**
R. Kidney						
Absolute	0.190 ± 0.006	0.193 ± 0.004	0.191 ± 0.004	0.180 ± 0.004	0.171 ± 0.002**	0.154 ± 0.004**
Relative	7.40 ± 0.14	7.73 ± 0.31	8.13 ± 0.23	7.59 ± 0.29	9.24 ± 0.10**	9.68 ± 0.39**
Liver						
Absolute	1.241 ± 0.045	1.316 ± 0.027	1.212 ± 0.050	1.194 ± 0.032	0.989 ± 0.018**	0.863 ± 0.059**
Relative	48.30 ± 1.19	52.68 ± 1.59	51.45 ± 1.98	50.15 ± 1.53	53.57 ± 1.30	54.12 ± 3.44
Lungs						
Absolute	0.186 ± 0.016	0.186 ± 0.013	0.185 ± 0.003	0.178 ± 0.007	0.153 ± 0.005	0.168 ± 0.016
Relative	7.17 ± 0.41	7.54 ± 0.74	7.95 ± 0.42	7.44 ± 0.24	8.29 ± 0.24	10.72 ± 1.23**
Spleen						
Absolute	0.076 ± 0.003	0.075 ± 0.002	0.073 ± 0.005	0.070 ± 0.005	0.052 ± 0.002**	0.037 ± 0.004**
Relative	2.96 ± 0.10	3.01 ± 0.12	3.10 ± 0.17	2.94 ± 0.19	2.78 ± 0.12	2.31 ± 0.26*
Thymus						
Absolute	0.052 ± 0.005	0.052 ± 0.004	0.044 ± 0.004	0.046 ± 0.004	0.036 ± 0.004*	0.025 ± 0.004**
Relative	2.04 ± 0.20	2.07 ± 0.17	1.82 ± 0.13	1.91 ± 0.16	1.94 ± 0.23	1.54 ± 0.24

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=7

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
n	10	9	10	10
Necropsy body wt	48.6 ± 1.2	49.3 ± 1.9	47.6 ± 1.3	46.6 ± 1.5
R. Kidney				
Absolute	0.442 ± 0.012	0.434 ± 0.025	0.414 ± 0.013	0.423 ± 0.015
Relative	9.09 ± 0.12	8.82 ± 0.38	8.77 ± 0.38	9.13 ± 0.37
Liver				
Absolute	2.355 ± 0.192	2.271 ± 0.187	2.123 ± 0.155	2.313 ± 0.331
Relative	48.48 ± 3.72	45.71 ± 2.73	45.02 ± 3.92	50.75 ± 8.67
Female				
n	8	10	9	10
Necropsy body wt	50.4 ± 2.9	54.8 ± 1.7	52.7 ± 2.1	49.3 ± 2.0
R. Kidney				
Absolute	0.264 ± 0.009	0.253 ± 0.007	0.261 ± 0.005	0.263 ± 0.009
Relative	5.30 ± 0.20	4.65 ± 0.18	5.00 ± 0.18	5.38 ± 0.20
Liver				
Absolute	1.616 ± 0.074	1.678 ± 0.045	1.949 ± 0.211	1.741 ± 0.072
Relative	32.28 ± 0.73	30.80 ± 0.90	36.88 ± 3.25	35.70 ± 1.77

[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
CLINICAL CHEMISTRY AND URINALYSIS RESULTS

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Core Study						
Male						
Clinical Chemistry						
n	10	10	9	10	10	10
Urea nitrogen (mg/dL)	21.4 ± 0.6	22.8 ± 0.6	22.3 ± 1.4	21.7 ± 0.9	21.2 ± 0.7	21.2 ± 0.9
Creatinine (mg/dL)	0.80 ± 0.13	0.70 ± 0.15	0.89 ± 0.11	1.00 ± 0.00	0.90 ± 0.10	1.00 ± 0.00
Glucose (mg/dL)	98 ± 6	123 ± 8	132 ± 17	100 ± 5	108 ± 7	106 ± 8
Total protein (g/dL)	7.0 ± 0.1	6.9 ± 0.1	6.6 ± 0.3[b]	6.9 ± 0.1	7.0 ± 0.1	7.1 ± 0.1
Albumin (g/dL)	5.5 ± 0.1	5.4 ± 0.1	5.4 ± 0.0[c]	5.4 ± 0.1	5.4 ± 0.1	5.5 ± 0.1
Globulin (g/dL)	1.5 ± 0.1	1.5 ± 0.1	1.4 ± 0.1[c]	1.5 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
A/G ratio	3.8 ± 0.2	3.5 ± 0.2	3.9 ± 0.2[c]	3.7 ± 0.2	3.4 ± 0.1	3.6 ± 0.2
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)	0.156 ± 0.015	0.150 ± 0.016	0.170 ± 0.012	0.156 ± 0.018[d]	0.161 ± 0.006	0.148 ± 0.012
Protein (mg/hr)	0.658 ± 0.058	0.620 ± 0.057	0.728 ± 0.037	0.606 ± 0.127[d]	0.861 ± 0.036*	0.839 ± 0.044*
Volume (mL/16 hr)	8.2 ± 0.8	9.6 ± 1.5	12.3 ± 1.6	13.1 ± 2.9	19.5 ± 1.9**	17.7 ± 1.5**
Specific gravity	1.029 ± 0.003	1.024 ± 0.003	1.023 ± 0.003	1.015 ± 0.003**	1.016 ± 0.001**	1.015 ± 0.001**
Female						
Clinical Chemistry						
n	10	10	9	8	10	10
Urea nitrogen (mg/dL)	20.9 ± 1.0	21.6 ± 0.4	20.8 ± 0.7	20.8 ± 0.9	20.0 ± 0.7	21.5 ± 0.6
Creatinine (mg/dL)	0.90 ± 0.10	0.90 ± 0.10	1.00 ± 0.00	0.63 ± 0.18	0.50 ± 0.17	0.70 ± 0.15
Glucose (mg/dL)	90 ± 5	100 ± 6	104 ± 11	98 ± 5	90 ± 3	108 ± 9
Total protein (g/dL)	7.1 ± 0.1	7.0 ± 0.1	6.8 ± 0.0	6.6 ± 0.1*	6.8 ± 0.1*	6.4 ± 0.1**
Albumin (g/dL)	5.6 ± 0.1	5.6 ± 0.1	5.3 ± 0.1**	5.3 ± 0.1**	5.4 ± 0.1**	5.2 ± 0.1**
Globulin (g/dL)	1.4 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.2 ± 0.1
A/G ratio	4.1 ± 0.2	3.9 ± 0.1	3.5 ± 0.2	4.0 ± 0.3	3.8 ± 0.2	4.5 ± 0.3
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)	0.091 ± 0.006	0.073 ± 0.009[d]	0.089 ± 0.006	0.089 ± 0.009	0.094 ± 0.008	0.100 ± 0.012
Protein (mg/hr)	0.037 ± 0.003[d]	0.029 ± 0.004[d]	0.035 ± 0.004	0.032 ± 0.002	0.043 ± 0.003	0.040 ± 0.008
Volume (mL/16 hr)	6.0 ± 0.6	10.2 ± 2.1	10.3 ± 1.0*	8.8 ± 0.8	9.7 ± 1.3	9.9 ± 2.1
Specific gravity	1.031 ± 0.005	1.020 ± 0.006	1.016 ± 0.002*	1.020 ± 0.002	1.020 ± 0.003	1.022 ± 0.004
Special Study						
Male						
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	30.4 ± 1.0[c]	31.8 ± 1.1[c]	29.6 ± 1.2[c]	30.1 ± 1.3	32.0 ± 1.5	32.3 ± 1.1
Day 15	26.2 ± 1.0	26.9 ± 0.9	25.4 ± 0.8	24.9 ± 0.8	28.8 ± 1.2	25.3 ± 0.9
Day 30	26.5 ± 0.4	26.7 ± 1.0	22.4 ± 0.7*	18.5 ± 0.7**	23.7 ± 0.9	27.4 ± 0.7
Day 60	30.9 ± 1.0[c]	23.1 ± 0.8**	25.1 ± 0.8	25.3 ± 1.0[b]	22.3 ± 1.7**[c]	28.6 ± 3.7
Week 13	24.5 ± 1.1[b]	22.3 ± 0.8[b]	23.0 ± 0.5[c]	22.4 ± 1.4[c]	17.9 ± 1.7**[c]	23.6 ± 0.9

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Male (continued)						
Clinical Chemistry (continued)						
n	10	10	10	10	10	10
Creatinine (mg/dL)						
Day 3	0.60 ± 0.16	0.33 ± 0.17[c]	0.33 ± 0.17[c]	0.20 ± 0.13	0.70 ± 0.15	0.60 ± 0.16
Day 15	0.30 ± 0.15	0.10 ± 0.10	0.50 ± 0.17	0.80 ± 0.13	0.50 ± 0.17	0.40 ± 0.16
Day 30	0.70 ± 0.15	0.60 ± 0.16	0.70 ± 0.15	0.30 ± 0.15	0.50 ± 0.17	0.70 ± 0.15
Day 60	0.78 ± 0.15[c]	0.89 ± 0.11[c]	0.90 ± 0.10	0.75 ± 0.16[b]	0.57 ± 0.20[c]	0.50 ± 0.17
Week 13	0.88 ± 0.13[b]	1.00 ± 0.00[b]	1.00 ± 0.00[c]	0.86 ± 0.14[c]	0.89 ± 0.11[c]	0.89 ± 0.11[c]
Glucose (mg/dL)						
Day 3	170 ± 7	166 ± 8[c]	180 ± 7[c]	178 ± 8	201 ± 8**	186 ± 7*
Day 15	190 ± 10	184 ± 9	174 ± 7	175 ± 7	168 ± 5	149 ± 6**
Day 30	170 ± 12	166 ± 5	160 ± 5	155 ± 4	174 ± 9	149 ± 7
Day 60	203 ± 21[c]	158 ± 15	219 ± 19	163 ± 18[b]	187 ± 14[b]	155 ± 18
Week 13	150 ± 20[b]	146 ± 11[b]	160 ± 8[c]	196 ± 23[c]	175 ± 16[c]	154 ± 17
Total protein (g/dL)						
Day 3	5.2 ± 0.1[c]	5.1 ± 0.1[b]	5.6 ± 0.1**[c]	5.7 ± 0.1**	5.7 ± 0.1**	5.7 ± 0.1**
Day 15	5.9 ± 0.1	5.9 ± 0.1	6.1 ± 0.1	6.2 ± 0.1	6.3 ± 0.0**	6.3 ± 0.1**
Day 30	6.4 ± 0.1	6.5 ± 0.1	6.1 ± 0.1	6.4 ± 0.1	6.4 ± 0.1	6.4 ± 0.1
Day 60	6.5 ± 0.1[c]	6.2 ± 0.2[c]	6.6 ± 0.1[c]	6.9 ± 0.1*[b]	6.8 ± 0.1[e]	7.0 ± 0.1**
Week 13	7.0 ± 0.1[b]	7.1 ± 0.1[b]	6.8 ± 0.1[c]	7.0 ± 0.1[c]	7.0 ± 0.1[b]	6.9 ± 0.1[b]
Urinalysis						
n	10	10	10	10	10	10
Glucose (mg/hr)						
Day 3	0.083 ± 0.004	0.075 ± 0.004	0.077 ± 0.005	0.078 ± 0.003	0.080 ± 0.004	0.065 ± 0.006
Day 15	0.138 ± 0.006[c]	0.136 ± 0.007	0.118 ± 0.007	0.146 ± 0.010[c]	0.156 ± 0.007	0.120 ± 0.009[c]
Day 30	0.165 ± 0.010	0.118 ± 0.006**	0.156 ± 0.005	0.183 ± 0.011	0.148 ± 0.007	0.155 ± 0.009
Day 60	0.196 ± 0.013	0.179 ± 0.003	0.156 ± 0.004**	0.156 ± 0.009*[c]	0.144 ± 0.006**	0.140 ± 0.008**
Week 13	0.184 ± 0.018[c]	0.177 ± 0.009[c]	0.154 ± 0.007[c]	0.162 ± 0.011[b]	0.136 ± 0.007*	0.129 ± 0.012*[b]
Protein (mg/hr)						
Day 3	0.071 ± 0.011	0.059 ± 0.009	0.069 ± 0.007	0.064 ± 0.007	0.068 ± 0.005	0.050 ± 0.006
Day 15	0.606 ± 0.032[c]	0.410 ± 0.054*	0.522 ± 0.047	0.544 ± 0.045[c]	0.450 ± 0.023**	0.168 ± 0.018**[c]
Day 30	0.797 ± 0.046	0.627 ± 0.039*	0.645 ± 0.041*	0.655 ± 0.029*	0.598 ± 0.034**	0.438 ± 0.026**
Day 60	0.637 ± 0.051	0.727 ± 0.036	0.754 ± 0.021	0.679 ± 0.047[c]	0.749 ± 0.049	0.820 ± 0.039*
Week 13	0.644 ± 0.050[c]	0.766 ± 0.058[c]	0.668 ± 0.038[c]	0.743 ± 0.059[b]	0.756 ± 0.055[c]	0.670 ± 0.073[b]
Volume (mL/16 hr)						
Day 3	10.3 ± 1.1	10.3 ± 1.3	9.0 ± 1.4	10.7 ± 1.2	8.9 ± 0.9	6.4 ± 0.9*
Day 15	17.7 ± 1.9[c]	12.8 ± 2.0	10.9 ± 1.4	14.7 ± 2.2	16.3 ± 1.1	7.4 ± 1.3**[c]
Day 30	14.4 ± 1.5	14.5 ± 1.8	9.1 ± 0.9*	12.2 ± 1.2	17.5 ± 1.9	18.5 ± 2.1
Day 60	14.2 ± 2.1	14.7 ± 1.9	14.0 ± 1.8	19.2 ± 2.7[c]	25.9 ± 1.9**	28.7 ± 3.1**
Week 13	16.2 ± 2.1[c]	13.3 ± 1.7[c]	11.8 ± 1.8[c]	16.9 ± 2.9[b]	24.5 ± 2.3	27.8 ± 3.5*[b]
Specific gravity						
Day 3	1.012 ± 0.001	1.011 ± 0.001	1.015 ± 0.002	1.012 ± 0.001	1.013 ± 0.001	1.016 ± 0.002
Day 15	1.021 ± 0.010[c]	1.018 ± 0.003	1.017 ± 0.001	1.015 ± 0.003	1.015 ± 0.001	1.026 ± 0.003**[c]
Day 30	1.018 ± 0.002	1.014 ± 0.002	1.025 ± 0.002	1.022 ± 0.002	1.014 ± 0.001	1.014 ± 0.001
Day 60	1.023 ± 0.002	1.018 ± 0.003	1.017 ± 0.002	1.014 ± 0.002*[c]	1.009 ± 0.001**	1.010 ± 0.001**
Week 13	1.017 ± 0.003[c]	1.021 ± 0.003[c]	1.020 ± 0.003[c]	1.016 ± 0.002[b]	1.010 ± 0.002*	1.009 ± 0.001*[b]

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Male (continued)						
Urine Concentration Study						
n	8	8	6	5	10	10
Volume (mL/4 hr)						
Day 4	1.600 ± 0.400[f]	1.567 ± 0.343[e]	0.458 ± 0.042**	1.000 ± 0.274*	0.563 ± 0.157*[g]	0.417 ± 0.083**[h]
Day 16	1.929 ± 0.352[c]	2.313 ± 0.499	0.700 ± 0.122*[f]	1.222 ± 0.222[c]	1.150 ± 0.107	0.850 ± 0.130*
Day 31	0.600 ± 0.158	1.229 ± 0.276[c]	0.875 ± 0.183[b]	1.100 ± 0.258[e]	0.786 ± 0.101[c]	1.233 ± 0.245[c]
Day 61	1.188 ± 0.188	1.188 ± 0.210	1.667 ± 0.511	0.486 ± 0.212[c]	1.150 ± 0.130	1.300 ± 0.153
Week 13	0.650 ± 0.218[g]	0.814 ± 0.314[c]	0.260 ± 0.098[f]	0.800 ± 0.200	0.167 ± 0.067[e]	0.789 ± 0.201[c]
Specific gravity						
Day 4	1.023 ± 0.008[g]	1.015 ± 0.009[g]	1.040 ± 0.003	1.035 ± 0.029[i]	1.050 ± 0.007[g]	1.071 ± 0.009*[h]
Day 16	1.039 ± 0.010[c]	1.037 ± 0.010	1.065 ± 0.008[f]	1.047 ± 0.008[c]	1.057 ± 0.002	1.067 ± 0.003**
Day 31	1.063 ± 0.005	1.026 ± 0.006**[c]	1.060 ± 0.005[b]	1.053 ± 0.006[e]	1.056 ± 0.006[b]	1.047 ± 0.003[c]
Day 61	1.067 ± 0.006	1.070 ± 0.003	1.058 ± 0.012	1.053 ± 0.008[c]	1.059 ± 0.003	1.047 ± 0.003**
Week 13	1.058 ± 0.009[g]	1.056 ± 0.010[c]	1.056 ± 0.010	1.043 ± 0.007	1.063 ± 0.003[e]	1.036 ± 0.005[c]
Female						
Clinical Chemistry						
n	9	10	9	10	10	10
Urea nitrogen (mg/dL)						
Day 3	31.2 ± 1.7	31.4 ± 1.7	33.1 ± 1.9	32.3 ± 1.3	32.0 ± 0.7	28.9 ± 1.2
Day 15	33.2 ± 0.9	31.7 ± 0.6	33.9 ± 1.2	34.8 ± 1.6	28.7 ± 0.6**	27.7 ± 0.7**
Day 30	25.8 ± 0.9	24.6 ± 0.5	28.7 ± 0.7	24.7 ± 1.1	24.3 ± 0.9	23.9 ± 0.9
Day 60	26.7 ± 1.0	24.8 ± 0.7	29.9 ± 1.0	29.6 ± 0.6	27.4 ± 1.3[c]	25.5 ± 1.1
Week 13	28.1 ± 0.7	28.7 ± 1.0	28.9 ± 1.2	27.6 ± 0.7	25.6 ± 0.8[c]	26.6 ± 0.9
Creatinine (mg/dL)						
Day 3	0.44 ± 0.18	0.10 ± 0.10	0.44 ± 0.18	0.30 ± 0.15	0.00 ± 0.00	0.00 ± 0.00
Day 15	0.22 ± 0.15	0.20 ± 0.13	0.67 ± 0.17	0.70 ± 0.15	0.30 ± 0.15	0.30 ± 0.15
Day 30	1.00 ± 0.00	0.60 ± 0.16*	0.56 ± 0.18*	0.60 ± 0.16	0.40 ± 0.16**	0.10 ± 0.10**
Day 60	0.78 ± 0.15	0.70 ± 0.15	1.00 ± 0.00	1.00 ± 0.00[c]	0.78 ± 0.15[c]	0.90 ± 0.10
Week 13	1.00 ± 0.00	0.90 ± 0.10	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00[c]	0.90 ± 0.10
Glucose (mg/dL)						
Day 3	175 ± 28	216 ± 33	155 ± 6	159 ± 5	153 ± 8	167 ± 6
Day 15	167 ± 6	159 ± 7	157 ± 9	157 ± 10	142 ± 8**	144 ± 7**
Day 30	146 ± 4	149 ± 4	135 ± 8	155 ± 5	145 ± 10	140 ± 4
Day 60	140 ± 8	143 ± 4	187 ± 20*	194 ± 12**	205 ± 18**[c]	177 ± 14**
Week 13	148 ± 6	153 ± 4	150 ± 10	169 ± 11	147 ± 6[c]	166 ± 13
Total protein (g/dL)						
Day 3	5.9 ± 0.1	6.2 ± 0.1	5.9 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	5.7 ± 0.1
Day 15	5.8 ± 0.1	5.9 ± 0.2	6.1 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	5.9 ± 0.1
Day 30	5.9 ± 0.1	6.0 ± 0.1	6.1 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	5.8 ± 0.1
Day 60	6.7 ± 0.1	6.7 ± 0.0	6.7 ± 0.1	6.5 ± 0.1[c]	6.8 ± 0.1[c]	6.6 ± 0.1
Week 13	6.9 ± 0.1	6.7 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	6.7 ± 0.1[c]	6.4 ± 0.1**

TABLE G1
Clinical Chemistry and Urinalysis Data for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol
(continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Special Study (continued)						
Female (continued)						
Urinalysis						
n	9	10	9	10	10	10
Glucose (mg/hr)						
Day 3	0.088 ± 0.005	0.088 ± 0.006	0.079 ± 0.005[j]	0.093 ± 0.010	0.059 ± 0.003**	0.053 ± 0.003**
Day 15	0.072 ± 0.005	0.074 ± 0.007[c]	0.065 ± 0.006	0.062 ± 0.007[c]	0.086 ± 0.006	0.081 ± 0.005
Day 30	0.094 ± 0.004	0.085 ± 0.004	0.122 ± 0.018[b]	0.107 ± 0.012	0.091 ± 0.012	0.105 ± 0.005
Day 60	0.109 ± 0.009	0.097 ± 0.010	0.091 ± 0.005[b]	0.078 ± 0.005**	0.076 ± 0.004**	0.091 ± 0.006*
Week 13	0.098 ± 0.008	0.096 ± 0.005	—[k]	0.077 ± 0.004	0.077 ± 0.002[c]	0.088 ± 0.005
Protein (mg/hr)						
Day 3	0.028 ± 0.002	0.027 ± 0.002	0.030 ± 0.004[j]	0.030 ± 0.002	0.030 ± 0.003	0.025 ± 0.002
Day 15	0.033 ± 0.004	0.031 ± 0.003[c]	0.031 ± 0.004	0.038 ± 0.005[c]	0.033 ± 0.002	0.033 ± 0.002
Day 30	0.030 ± 0.002[b]	0.034 ± 0.003	0.033 ± 0.007[b]	0.029 ± 0.003	0.034 ± 0.004	0.039 ± 0.004[c]
Day 60	0.033 ± 0.002	0.035 ± 0.005[c]	0.044 ± 0.004[b]	0.041 ± 0.003	0.035 ± 0.005	0.044 ± 0.006
Week 13	0.055 ± 0.006	0.047 ± 0.003	—	0.039 ± 0.004	0.038 ± 0.004[c]	0.041 ± 0.003
Volume (mL/16 hr)						
Day 3	13.2 ± 2.1[j]	13.2 ± 1.2	13.5 ± 1.5[j]	15.7 ± 2.4	14.6 ± 1.0	6.7 ± 1.0*
Day 15	11.9 ± 1.7	10.2 ± 1.7	10.8 ± 1.4	13.7 ± 2.9[c]	12.6 ± 1.5	11.8 ± 1.1
Day 30	12.8 ± 1.2	12.0 ± 1.6	13.1 ± 1.4	10.0 ± 2.2	14.4 ± 1.2	12.7 ± 1.6
Day 60	10.2 ± 1.4	10.4 ± 1.6	14.1 ± 1.9[b]	14.0 ± 2.3	11.8 ± 1.4	14.7 ± 1.2
Week 13	8.9 ± 1.0	11.3 ± 1.4	—	13.4 ± 1.5	12.7 ± 2.0[c]	11.0 ± 1.2
Specific gravity						
Day 3	1.011 ± 0.002[j]	1.008 ± 0.001	1.017 ± 0.010[j]	1.008 ± 0.001	1.008 ± 0.000	1.017 ± 0.002
Day 15	1.013 ± 0.001	1.016 ± 0.003	1.014 ± 0.002	1.015 ± 0.003[c]	1.015 ± 0.002	1.016 ± 0.002
Day 30	1.012 ± 0.001	1.013 ± 0.001	1.016 ± 0.002	1.026 ± 0.006	1.012 ± 0.001	1.016 ± 0.002
Day 60	1.018 ± 0.002	1.017 ± 0.002	1.012 ± 0.001**[b]	1.016 ± 0.004*	1.013 ± 0.002*	1.012 ± 0.001*
Week 13	1.018 ± 0.002	1.015 ± 0.001	—	1.011 ± 0.001**	1.013 ± 0.001[c]	1.015 ± 0.001
Urine Concentration Study						
n	5	4	5	6	7	9
Volume (mL/4 hr)						
Day 4	0.900 ± 0.100	0.750 ± 0.144	0.600 ± 0.100*	0.700 ± 0.122[f]	0.643 ± 0.092*	0.611 ± 0.073*
Day 16	0.371 ± 0.123[c]	0.280 ± 0.092[f]	0.586 ± 0.120[c]	0.588 ± 0.134[b]	0.917 ± 0.201*[e]	0.789 ± 0.140*
Day 31	0.500 ± 0.000[g]	0.625 ± 0.125	0.833 ± 0.167[h]	1.333 ± 0.333**	0.571 ± 0.118	0.944 ± 0.227
Day 61	0.100 ± 0.000[h]	0.400 ± 0.125[c]	0.340 ± 0.098	0.467 ± 0.088*[c]	0.167 ± 0.067[e]	0.383 ± 0.147[e]
Week 13	0.680 ± 0.461	0.100 ± 0.000**[f]	0.550 ± 0.450[i]	0.183 ± 0.065	0.788 ± 0.234[b]	1.100 ± 0.187*[f]
Specific gravity						
Day 4	1.066 ± 0.004	1.076 ± 0.004	1.067 ± 0.005	1.064 ± 0.011[f]	1.077 ± 0.003	1.064 ± 0.006
Day 16	1.074 ± 0.003[c]	1.075 ± 0.003[f]	1.068 ± 0.005[c]	1.055 ± 0.010[b]	1.047 ± 0.009[e]	1.060 ± 0.006
Day 31	1.061 ± 0.013	1.067 ± 0.007	1.060 ± 0.013[h]	1.053 ± 0.009	1.067 ± 0.008	1.054 ± 0.008
Day 61	1.072 ± 0.004[h]	1.033 ± 0.009**[c]	1.062 ± 0.006	1.050 ± 0.006[c]	1.046 ± 0.011[e]	1.063 ± 0.004[e]
Week 13	1.048 ± 0.014	1.037 ± 0.009[e]	1.035 ± 0.010[i]	1.048 ± 0.008[c]	1.059 ± 0.007[b]	1.061 ± 0.008[f]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8 [c] n=7 [d] n=9 [e] n=6 [f] n=5 [g] n=4 [h] n=3 [i] n=2 [j] n=10
[k] No measurements taken at this exposure level

TABLE G2
Clinical Chemistry and Urinalysis Data for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	625 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
Clinical Chemistry						
n	6	8	9	7	8	5
Urea nitrogen (mg/dL)	32.0 ± 3.6[b]	24.6 ± 1.5	28.0 ± 1.5	35.8 ± 2.9[c]	46.4 ± 5.9	72.3 ± 15.1*[d]
Glucose (mg/dL)	123 ± 8[b]	146 ± 14	162 ± 12	162 ± 14[c]	141 ± 18	146 ± 18[d]
Total protein (g/dL)	5.8 ± 0.1	5.9 ± 0.1	5.5 ± 0.2	5.8 ± 0.1[e]	5.7 ± 0.1	5.8 ± 0.2[d]
Albumin (g/dL)	3.8 ± 0.1	4.0 ± 0.1	3.6 ± 0.2	3.8 ± 0.1	3.8 ± 0.1	4.0 ± 0.2
Globulin (g/dL)	2.0 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1
A/G ratio	1.9 ± 0.1	2.1 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	2.1 ± 0.2
Urinalysis						
n	4	3	9	10	10	4
Glucose (mg/hr)	0.051 ± 0.014	0.024 ± 0.011	0.036 ± 0.007	0.025 ± 0.004	0.038 ± 0.004[c]	0.034 ± 0.004
Protein (mg/hr)	0.364 ± 0.062	0.148 ± 0.065	0.264 ± 0.051	0.228 ± 0.045	0.166 ± 0.028*	0.075 ± 0.020**
Volume (mL/24 hr)	3.63 ± 0.80	4.17 ± 1.69	3.06 ± 0.55	2.72 ± 0.55[c]	2.00 ± 0.17	2.25 ± 0.43
Specific gravity	1.020 ± 0.004	1.005 ± 0.003	1.016 ± 0.003	1.017 ± 0.004	1.023 ± 0.002	1.018 ± 0.001
Female						
Clinical Chemistry						
n	9	7	9	7	8	5
Urea nitrogen (mg/dL)	21.9 ± 0.9	24.8 ± 2.7[e]	22.6 ± 1.4	26.0 ± 3.0[e]	27.6 ± 1.7*[c]	37.8 ± 3.1**
Glucose (mg/dL)	151 ± 10	182 ± 13[e]	151 ± 7	148 ± 8[e]	130 ± 11[c]	118 ± 23
Total protein (g/dL)	6.0 ± 0.1	5.8 ± 0.1	6.4 ± 0.1	6.1 ± 0.1	6.1 ± 0.1[c]	6.4 ± 0.2
Albumin (g/dL)	4.2 ± 0.1	4.0 ± 0.1	4.5 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.1
Globulin (g/dL)	1.8 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	2.0 ± 0.2
A/G ratio	2.3 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.3 ± 0.1	2.5 ± 0.2	2.3 ± 0.3
Urinalysis						
n	9	7	7	9	9	6
Glucose (mg/hr)	0.043 ± 0.005	0.039 ± 0.005	0.041 ± 0.009	0.044 ± 0.009	0.048 ± 0.005	0.022 ± 0.005
Protein (mg/hr)	0.147 ± 0.027	0.171 ± 0.024	0.154 ± 0.037	0.161 ± 0.027	0.112 ± 0.011	0.016 ± 0.003**
Volume (mL/24 hr)	3.7 ± 0.5	3.4 ± 0.6	3.5 ± 0.8	3.0 ± 0.6	3.5 ± 0.3	2.2 ± 0.6
Specific gravity	1.016 ± 0.002	1.016 ± 0.002	1.016 ± 0.002	1.020 ± 0.003	1.018 ± 0.002	1.008 ± 0.002

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=7
[c] n=9
[d] n=6
[e] n=8

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Rats in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male				
n	10	10	10	10
Weights (g)				
Necropsy body wt.	334 ± 6	308 ± 10*	299 ± 8**	255 ± 7**
R. cauda	0.169 ± 0.011	0.166 ± 0.007	0.175 ± 0.008	0.162 ± 0.008
R. epididymis	0.509 ± 0.016	0.519 ± 0.024	0.508 ± 0.020	0.503 ± 0.016
R. testis	1.492 ± 0.027	1.443 ± 0.035	1.411 ± 0.038	1.360 ± 0.036**
Epididymal spermatozoal parameters				
Motility (%)	97.33 ± 0.78	97.03 ± 0.71	97.48 ± 0.53	96.96 ± 1.05
Concentration (10^6/g cauda epididymal tissue)	558.2 ± 42.8	524.6 ± 27.3	552.0 ± 32.1	646.8 ± 50.7
Normal (per 500 sperm)	496.3 ± 0.5	495.7 ± 0.4	493.9 ± 1.4	495.4 ± 0.6
Abnormal (%)	0.740 ± 0.099	0.860 ± 0.079	1.220 ± 0.284	0.920 ± 0.116
Amorphous (per 500 sperm)	0.300 ± 0.153	0.500 ± 0.224	0.600 ± 0.221	0.600 ± 0.221
Excessive hook (per 500 sperm)	1.400 ± 0.476	0.900 ± 0.379	1.500 ± 0.764	1.500 ± 0.269
No hook (per 500 sperm)	1.20 ± 0.25	2.30 ± 0.47	3.10 ± 0.82	1.70 ± 0.33
Pin-head (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Short-headed (per 500 sperm)	0.800 ± 0.249	0.500 ± 0.167	0.900 ± 0.277	0.800 ± 0.200
Two tails or heads (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Female				
n	10	10	10	10
Necropsy body wt. (g)	200 ± 6	184 ± 3**	174 ± 6**	163 ± 2**
Estrous cycle length (days)	4.70 ± 0.21	4.70 ± 0.15	5.00 ± 0.15	5.56 ± 0.47[b]
Estrous stages (% of cycle)				
Diestrus	27.1	28.6	27.1	27.1
Proestrus	14.3	14.3	17.1	20.0
Estrus	27.1	27.1	21.4	21.4
Metestrus	31.4	30.0	34.3	31.4

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

TABLE H2
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 13-Week Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male				
n	10	10	10	7
Weights (g)				
Necropsy body wt. (g)	27.8 ± 1.6	25.4 ± 0.4	21.6 ± 0.4**	17.4 ± 0.4**
R. cauda	0.023 ± 0.001	0.020 ± 0.002	0.017 ± 0.001**	0.012 ± 0.001**
R. epididymis	0.086 ± 0.005	0.074 ± 0.005	0.055 ± 0.002**	0.048 ± 0.003**
R. testis	0.122 ± 0.003	0.122 ± 0.004	0.114 ± 0.002	0.102 ± 0.005**
Epididymal spermatozoal parameters				
Motility (%)	90.17 ± 0.93	92.96 ± 2.12	90.05 ± 1.74	85.79 ± 9.36
Concentration (10^6/g cauda epididymal tissue)	988.1 ± 64.0	1,065.3 ± 110	1,163.2 ± 116	1,334.8 ± 157
Normal (per 500 sperm)	494.7 ± 0.7	494.2 ± 1.1	494.4 ± 0.8	495.1 ± 0.9
Abnormal (%)	1.060 ± 0.140	1.160 ± 0.229	0.940 ± 0.133	0.971 ± 0.177
Amorphous (per 500 sperm)	2.50 ± 0.56	2.40 ± 1.01	1.90 ± 0.28	1.71 ± 0.52
Banana (per 500 sperm)	2.10 ± 0.28	2.30 ± 0.42	1.70 ± 0.47	2.43 ± 0.30
Blunt hook (per 500 sperm)	0.400 ± 0.267	0.500 ± 0.224	0.700 ± 0.396	0.143 ± 0.143
Pin-head (per 500 sperm)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.143 ± 0.143
Short-headed (per 500 sperm)	0.200 ± 0.133	0.200 ± 0.133	0.200 ± 0.133	0.143 ± 0.143
Two tails or heads (per 500 sperm)	0.000 ± 0.000	0.200 ± 0.133	0.100 ± 0.100	0.286 ± 0.286
Female				
n	9	9	9	9
Necropsy body wt. (g)	25.8 ± 1.1	23.9 ± 0.7	18.5 ± 0.3**	16.0 ± 0.6**
Estrous cycle length (days)	4.00 ± 0.00[b]	4.00 ± 0.00[c]	4.11 ± 0.11[c]	5.43 ± 0.48[b]
Estrous stages (% of cycle)				
Diestrus	32.9	22.9	20.0	25.7
Proestrus	18.6	21.4	12.9	12.9
Estrus	18.6	21.4	31.4	41.4
Metestrus	20.0	24.3	25.7	18.6
Unclear diagnosis	10.0	10.0	10.0	1.4

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Data are presented as mean ± standard error.
[b] Estrous cycle was longer than 7 days or was unclear in 3 of 10 animals.
[c] Estrous cycle was longer than 7 days or was unclear in 1 of 10 animals.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

2,2-Bis(bromomethyl)-1,3-propanediol was obtained from Dow Chemical Company (Rolling Meadows, IL) in one lot (840429-162), which was used during the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the 2,2-bis(bromomethyl)-1,3-propanediol studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a fine white powder, was identified as 2,2-bis(bromomethyl)-1,3-propanediol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of 2,2-bis(bromomethyl)-1,3-propanediol (Figures I1 and I2).

The purity was determined by elemental analyses, Karl Fischer water analysis, thin-layer chromatography (TLC), and gas chromatography. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) toluene:methanol (80:20), and 2) chloroform:acetone (80:20) with 3-chloro-1,2-propanediol as a reference standard. Plates were examined under visible and ultraviolet light at 254 nm and 366 nm and with a spray of 0.5% potassium permanganate in 1N sodium hydroxide. Gas chromatography was performed using a flame ionization detector and a nitrogen carrier gas. Two systems were used:

A) Tenax GC 60/80 mesh column with a nitrogen flow rate of 17 mL/minute and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and

B) 3% SP-2250 on 100/120 Supelcoport column with a nitrogen flow rate of 70 mL/minute and an isothermal oven temperature of 195° C.

Elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values for 2,2-bis(bromomethyl)-1,3-propanediol. Karl Fischer water analysis indicated 0.3% ± 0.1% water. TLC by each system indicated a major spot and one impurity. Gas chromatography by system A indicated one major peak and three impurities with areas greater than or equal to 0.1%, and totaling 1.6% relative to the major peak. Gas chromatography using system B indicated a major peak and four impurities with areas greater than or equal to 0.1%, and totaling 3.0% relative to the major peak.

High-performance liquid chromatography (HPLC) analyses were also conducted. HPLC was performed using a DuPont Zorbax ODS column with an isocratic solvent system of water:methanol (25:75) at a flow rate of 1.0 mL/minute and indicated a major peak and nine impurities with areas greater than 0.1% and totaling 21.2%. Samples were also analyzed with solvent systems containing 80% and 100% methanol as well as methanol:water (30:70). No additional impurities with relative areas greater than 1% were observed.

Five impurity peaks with areas of 1% or greater were detected in lot 840429-162. The impurities were further characterized by HPLC and direct inlet mass spectrometry (DIMS). The major peak and four of the impurities with peak areas greater than 1% were isolated by HPLC as described above, but with a water:methanol (38:62) solvent system. These impurities were then characterized by analysis with DIMS with electron impact, positive chemical ionization, and negative chemical ionization. Two impurities, 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%) and 2,2,-bis(bromomethyl)-1-bromo-3-hydroxypropane (6.9%), were identified. One impurity (1%) was tentatively identified as a dimer of the

parent chemical. Another impurity peak (2.8%) consisted of multiple components, including a structural isomer and a dimer of the parent compound (Figure I3).

A specific quantitation for an identified impurity was performed if a standard was available. The impurity identified as 1,1-bis(bromomethyl)-1-bromo-3-hydroxypropane was quantitated against a standard obtained from Velsicol Chemical Company (Chicago, IL), by HPLC. HPLC as described previously, but with water:methanol (35:65) solvent system and velerophenone as an internal standard, indicated 7.5% ± 0.1% 2,2-bis(bromomethyl)-1-bromo-3-hydroxypropane.

The impurity identified as pentaerythritol (reactant in the synthesis of 2,2-bis(bromomethyl)-1,3-propanediol) was quantitated against a pentaerythritol standard solution prepared by the analytical chemistry laboratory. HPLC as described with a water:methanol (25:75) solvent system detected a peak in the chromatographic profile of lot 840429-162 with a retention time that was consistent with that of the concomitantly analyzed pentaerythritol standard. Interference from the solvent was observed and the impurity peak could not be accurately quantitated. The amount of pentaerythritol observed was estimated at 0.2% by peak are comparison. The overall purity for lot 840429-162 was determined to be approximately 78.6%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Stability studies were performed using gas chromatography system B as described previously for the purity analysis, except with a carrier gas flow rate of 60 mL/minute and an isothermal oven temperature of 150° C. These studies indicated that 2,2-bis(bromomethyl)-1,3-propanediol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in sealed containers, protected from light. Stability was monitored monthly during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 13-week and 2-year feed studies were prepared weekly by mixing the appropriate quantities of dry 2,2-bis(bromomethyl)-1,3-propanediol with feed in a Udy® Cyclone Sample Mill to produce a premix. Premixes were then blended with more feed in a Patterson-Kelley Twin Shell® blender for 15 minutes, with an intensifier bar used for the initial 5 minutes. The formulations were stored in sealed, double plastic bags for no longer than 21 days (13-week studies) or 15 days (2-year studies) at −20° C.

Homogeneity and stability analyses of the dosed feed preparations were conducted by the analytical chemistry laboratory. For the homogeneity studies, samples of 630 and 20,000 ppm formulations were analyzed. Samples (10 g) of the dose formulations were extracted with 25 mL (630 ppm extract) or 100 mL (20,000 ppm extract) acetonitrile:water (90:10) and shaken for 30 minutes. The extracts were then centrifuged for 5 minutes. The 20,000 ppm extract was then separated into 5 mL aliquots and diluted to 23 mL with the acetonitrile:water solution. To remove water from the extracts, 5 mL portions of the diluted 20,000 ppm extract and the undiluted 630 ppm extract were combined with 3 g of anhydrous sodium sulfate and allowed to stand for 15 minutes with periodic shaking. Aliquots (3 mL) of the anhydrous solution were added to 3 mL of derivatizing reagent (reagent-grade acetic anhydride in a solution of hexadecane diluted with pyridine) and then heated in a 50° C water bath for 15 minutes. Portions of the resulting solutions were then analyzed by gas chromatography using a flame ionization detector and 10% SP-2100 on 100/120 mesh Supelcoport and a nitrogen carrier gas at a flow rate of 30 mL/minute and an oven temperature program of 160° C for 20 minutes, then 160° C to 200°C at 10° C/minute with a hold for 10 minutes at 200° C. For the stability analyses, 630 and 20,000 ppm were

prepared, stored up to 21 days in the dark at 5° or −20° C or under animal room conditions, then analyzed by the same gas chromatography method described for the homogeneity analysis. Homogeneity was confirmed; stability of the 630 ppm formulation was confirmed for at least 3 weeks when stored in sealed containers in the dark at −20° C. Based on these observations, the dose formulations were stored in the dark at −20° C for no more than 3 weeks.

Periodic analyses of the dose formulations of 2,2-bis(bromomethyl)-1,3-propanediol were conducted at the study laboratory with gas chromatography using a flame ionization detector and 10% SP-2100 on Supelcoport 100/120 mesh and a nitrogen carrier gas at a flow rate of 30 mL/minute and an isothermal oven temperature of 165° C for 15 minutes, then 165° to 200° C at 10° C per minute and 200° C for 7 minutes. For the 13-week studies, dose formulations were analyzed at the beginning, in the middle, and at the end of the studies (Table I2). During the 2-year studies, formulations were analyzed at least every 10 weeks (Table I3). All the dose formulations analyzed for rats and mice were within 10% of the target concentration during the 13-week studies. During the 2-year rat study, dose formulations were within 10% of the target concentrations 88% (75/85) of the time. The dose formulations found to be outside the acceptable limits were remixed and reanalyzed, and all formulations were within 10% of the target concentration except one (−11%). The 2-year mouse study dose formulations were within 10% of the target concentrations 98% (44/45) of the time. Results of periodic referee analyses performed by the analytical chemistry laboratory agreed with the results obtained by the study laboratory (Table I4).

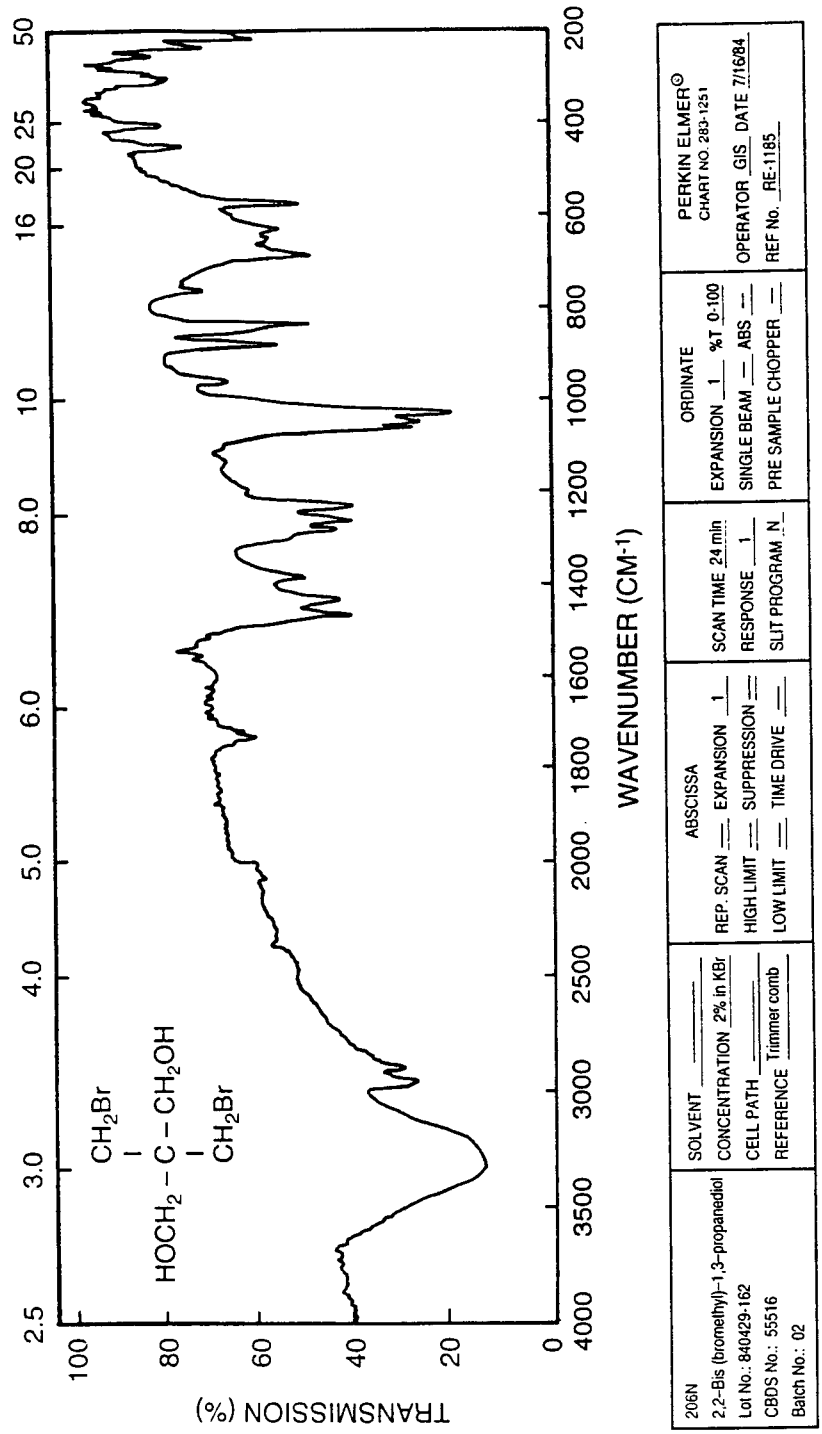


FIGURE I1
Infrared Absorption Spectrum of 2,2-Bis(bromomethyl)-1,3-propanediol

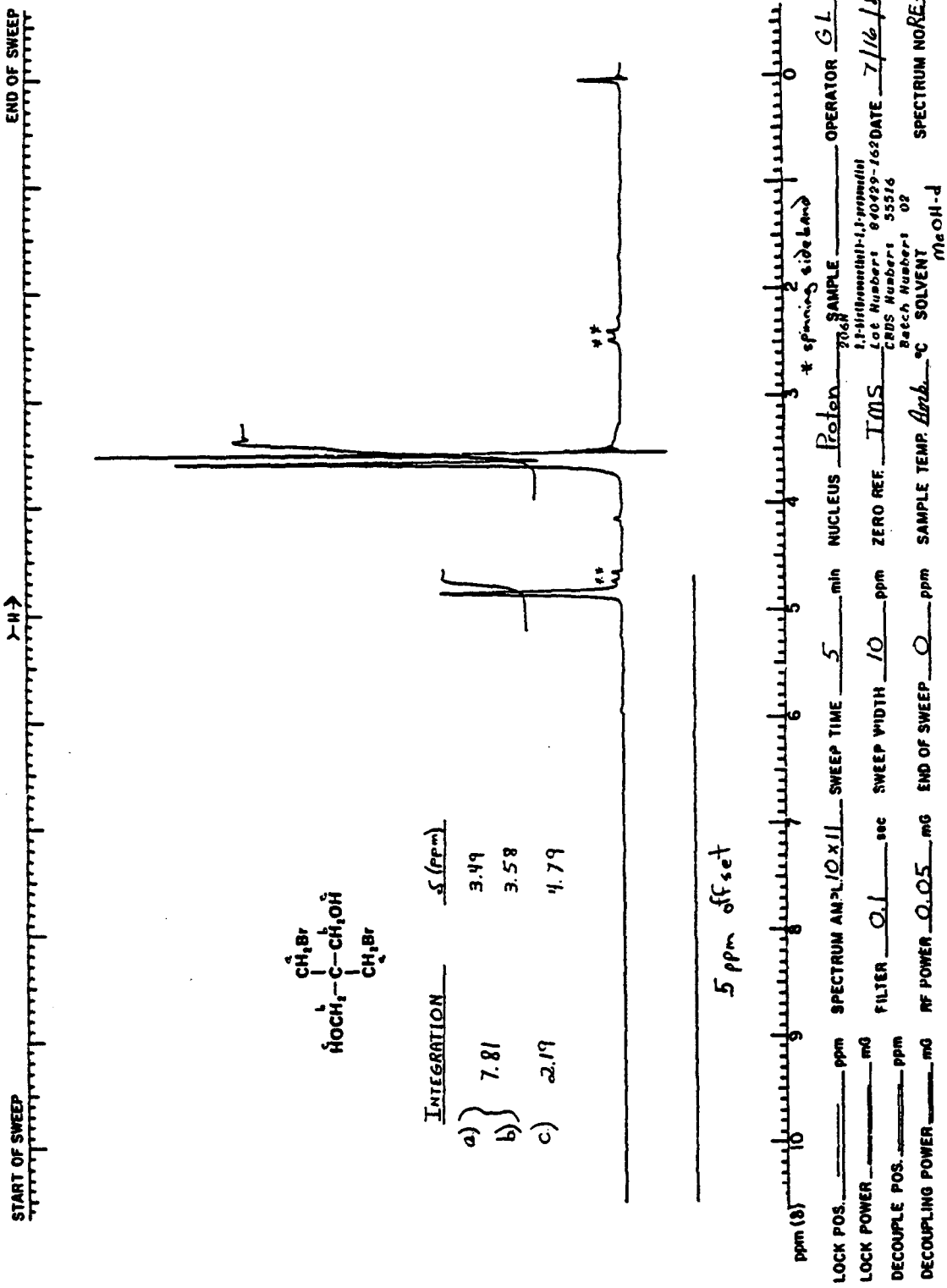
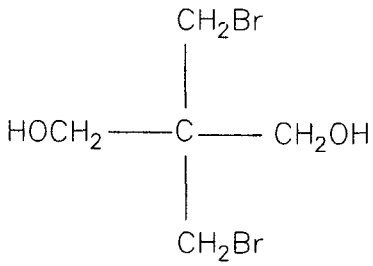
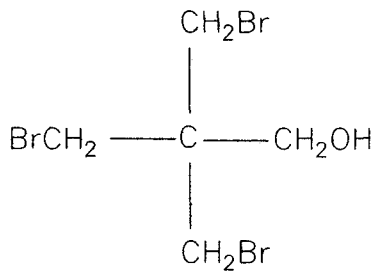


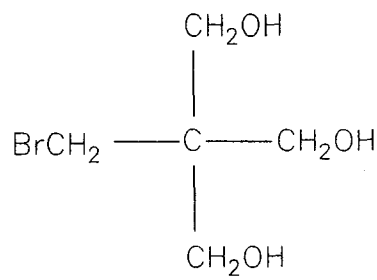
FIGURE I2
Nuclear Magnetic Resonance Spectrum of 2,2-Bis(bromomethyl)-1,3-propanediol



78.6% 2,2-Bis(bromomethyl)-1,3-propanediol
(Dibromoneopentyl Glycol)



6.9% 2,2-Bis(bromomethyl)-1-bromo-3-hydroxypropane
(Tribromoneopentyl Alcohol)



6.6% 2,2-Bis(hydroxymethyl)-1-bromo-3-hydroxypropane
(Monobromoneopentyltriol)

FIGURE I3
Structures and Names of the Parent Compound and Major Impurities

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

13-Week Studies	2-Year Studies
Preparation	
A premix of feed and 2,2-bis(bromomethyl)-1,3-propanediol was prepared by milling mixtures of the chemical and feed in a Udy® Cyclone Sample Mill. The premix was then layered into the remaining feed and blended in a Patterson-Kelly twin-shell blender with the intensifier bar on for 5 minutes and off for 10 minutes. Doses were prepared weekly.	Same as 13-week studies
Chemical Lot Number	
840429-162	840429-162
Maximum Storage Time	
3 weeks	2 weeks
Storage Conditions	
Stored in sealed containers protected from light at −20° C in double plastic bags	Same as 13-week studies
Study Laboratory	
American Biogenics Corporation (Woburn, MA)	Southern Research Institute (Birmingham, AL)
Referee Laboratory	
Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
4 February 1986	5 February 1986	20	19.91[b]	−1
		20	19.82[c]	−1
		20	19.55[d]	−2
8 April 1986	9 April 1986	1.25	1.199	−4
		1.25	1.186[e]	−5
		2.5	2.372	−5
		2.5	2.459[e]	−2
		5	4.705	−6
		5	4.902[e]	−2
9 April 1986	11 April 1986	10	9.74	−3
		20	20.26	+1
20 May 1986	21 May 1986	1.25	1.274	+2
		1.25	1.242	−1
		2.5	2.474	−1
		2.5	2.513	+1
		5	4.968	−1
		5	4.917	−2
		10	9.91	−1
		10	9.76	−2
		20	19.57	−2
		20	19.59	−2
28 July 1986	29 July 1986	1.25	1.176	−6
		2.5	2.414	−3
		5	5.018	0
28 July 1986	14 August 1986	10	9.81	−2
		20	19.66	−2
Mice				
8 April 1986	9 April 1986	0.625	0.6652	+6
		0.652	0.6221[e]	−1
		1.25	1.199	−4
		1.25	1.186[e]	−5
		2.5	2.372	−5
		2.5	2.459[e]	−2
		5	4.705	−6
		5	4.902[e]	−2
9 April 1986	11 April 1986	10	9.74	−3

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	% Difference from Target
Mice (continued)				
20 May 1986	21 May 1986	0.625	0.6301	+1
		1.25	1.274	+2
		2.5	2.474	−1
		5	4.968	−1
21 May 1986	22 May 1986	10	9.91	−1
30 June 1986	1 July 1986	0.625	0.6072	−3
		1.25	1.212	−3
		2.5	2.476	−1
		5	4.989	0
1 July 1986	2 July 1986	10	9.83	−2

[a] Results of duplicate analyses. For rats, 20 mg/g = 20,000 ppm. For mice, 0.625 mg/kg = 625 ppm; for rats and mice, 1.25 mg/g = 1,250 ppm; 2.5 mg/g = 2,500 ppm; 5 mg/g = 5,000 ppm; 10 mg/g = 10,000 ppm.
[b] Sample selection from top left of twin-shell blender
[c] Sample selection from top right of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of single analysis by internal standard method

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
Rats				
27 February 1989	28 February - 3 March 1989	20	20.4[b]	+2
		20	19.5[c]	−2
		20	20.1[d]	+1
17 March 1989	20-21 March 1989	2.5	2.66	+6
		2.5	2.70	+8
		5	5.50	+10
		5	4.26	−15
		10	10.4	+4
		10	10.1	+1
		20	19.6	−2
		20	21.2	+6
23 March 1989[e]	24 March 1989	5	5.07	+1
18 May 1989	19, 20, and 22 May 1989	2.5	2.35	−6
		2.5	2.42	−3
		5	5.13	+3
		5	5.44	+9
		10	10.2	+2
		10	10.2	+2
		20	20.8	+4
		20	20.3	+2
27 July 1989	27-29 July 1989	2.5	2.48	−1
		2.5	2.52	+1
		5	4.99	0
		5	4.90	−2
		10	10.0	0
		10	10.1	+1
7 September 1989	8-9 September 1989	2.5	2.56	+2
		2.5	2.50	0
		5	5.22	+4
		5	5.23	+5
		10	10.4	+4
		10	14.8	+48
13 September 1989[e]	14 September 1989	10	10.1	+1
2 November 1989	2-4 November 1989	2.5	2.48	−1
		2.5	2.68	+7
		5	5.25	+5
		5	5.18	+4
		10	10.2	+2
		10	10.5	+5

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Rats (continued)				
14 December 1989	14-16 December 1989	2.5	2.15	−14
		2.5	2.20	−12
		5	4.88	−2
		5	4.88	−2
		10	10.3	+3
		10	10.3	+3
18 December 1989[e]	19 December 1989	2.5	2.52	+1
		2.5	2.55	+2
8 February 1990	8-13 February 1990	2.5	2.47	−1
		2.5	2.47	−1
		5	4.92	−2
		5	5.02	0
		10	10.4	+4
		10	9.92	−1
5 April 1990	5-7 April 1990	2.5	2.57	+3
		2.5	2.90	+16
		5	5.62	+12
		5	5.42	+8
		10	9.98	0
		10	10.2	+2
10 April 1990[e]	10 April 1990	2.5	2.40	−4
		5	3.80	−24
11 April 1990[e]	12-13 April 1990	5	4.47	−11
21 June 1990	21-25 June 1990	2.5	2.62	+5
		2.5	2.64	+6
		5	4.74	−5
		5	5.09	+2
		10	10.0	0
		10	10.2	+2
16 August 1990	16-18 August 1990	2.5	2.46	−2
		2.5	2.65	+6
		5	5.11	+2
		5	5.03	+1
		10	10.0	0
		10	10.2	+2
25 October 1990	25, 26, and 29-31 October 1990	2.5	2.45	−2
		2.5	2.38	−5
		5	4.88	−2
		5	4.23	−16
		10	11.3	+13
		10	12.1	+21

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Rats (continued)				
1 November 1990[e]	1-2 November 1990	5	4.90	−2
		10	9.82	−2
		10	9.91	−1
3 January 1991	3-6 January 1991	2.5	2.42	−3
		2.5	2.40	−4
		5	4.92	−2
		5	5.19	+4
		10	10.3	+3
		10	10.1	+1
7 March 1991	7-9 March 1991	2.5	2.52	+1
		2.5	2.42	−3
		5	5.16	+3
		5	5.40	+8
		10	11.1	+11
		10	9.4	−6
12 March 1991[e]	12-13 March 1991	10	10.4	+4
Mice				
27 February 1989	28 February - 3 March 1989	0.312	0.321[b]	+3
		0.312	0.313[c]	0
		0.312	0.311[d]	0
7-8 March 1989	8-9 March 1989	0.312	0.336	+8
		0.312	0.332	+6
		0.625	0.663	+6
		0.625	0.648	+4
		1.25	1.32	+6
		1.25	1.31	+5
18 May 1989	19, 20, and 22 May 1989	0.312	0.324	+4
		0.625	0.610	−2
		1.25	1.20	−4
27 July 1989	27-29 July 1989	0.312	0.321	+3
		0.625	0.599	−4
		1.25	1.24	−1
7 September 1989	8-9 September 1989	0.312	0.332	+6
		0.625	0.626	0
		1.25	1.24	−1
2 November 1989	2-4 November 1989	0.312	0.320	+3
		0.625	0.618	−1
		1.25	1.22	−2

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
Mice (continued)				
14 December 1989	14-16 December 1989	0.312	0.334	+7
		0.625	0.612	−2
		1.25	1.24	−1
8 February 1990	8-13 February 1990	0.312	0.327	+5
		0.625	0.630	+1
		1.25	1.22	−2
5 April 1990	5-7 April 1990	0.312	0.311	0
		0.625	0.617	−1
		1.25	1.27	+2
21 June 1990	21-25 June 1990	0.312	0.324	+4
		0.625	0.586	−6
		1.25	1.16	−7
16 August 1990	16-18 August 1990	0.312	0.319	+2
		0.625	0.659	+6
		1.25	1.22	−2
25 October 1990	25, 26, and 29-31 October 1990	0.312	0.322	+3
		0.625	0.654	+5
		1.25	1.24	−1
3 January 1991	3-6 January 1991	0.312	0.312	0
		0.625	0.619	−1
		1.25	1.26	+1
7 March 1991	7-9 March 1991	0.312	0.226	−28
		0.625	0.633	+1
		1.25	1.26	+1
12 March 1991[e]	12-13 March 1991	0.312	0.285	−9

[a] Results of duplicate analyses. For rats, 2.5 mg/g = 2,500 ppm; 5 mg/g = 5,000 ppm; 10 mg/g = 10,000 ppm; 20 mg/g = 20,000 ppm. For mice, 0.312 mg/g = 312 ppm; 0.625 mg/g = 625 ppm; 1.25 mg/g = 1,250 ppm.
[b] Sample selection from top right of twin-shell blender
[c] Sample selection from top left of twin-shell blender
[d] Sample selection from bottom of twin-shell blender
[e] Results of remix

TABLE I4
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Date Prepared	Target Concentration (mg/g)	Determined Concentration (mg/g) Study Laboratory[a]	Determined Concentration (mg/g) Referee Laboratory[b]
13-Week Studies (American Biogenics Corp.)			
Rats			
8 April 1986	1.25	1.199	1.20 ± 0.04
Mice			
1 July 1986	10	9.83	9.845 ± 0.143
2-Year Studies (Southern Research Institute)			
Rats			
17 March 1989	10	10.3[c]	10.9 ± 1.06
8 February 1990	2.5	2.47	2.51 ± 0.13
Mice			
8 March 1989	0.625	0.656[c]	0.663 ± 0.02

[a] Results of duplicate analyses. For rats and mice, 0.625 mg/g = 625 ppm; 1.25 mg/g = 1,250 ppm; 2.5 mg/g = 2,500 ppm; 10 mg/g = 10,000 ppm.
[b] Results of triplicate analyses (mean ± standard error)
[c] Average of results from two sets of duplicate analyses

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF 2,2-BIS(BROMOMETHYL)-1,3-PROPANEDIOL

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		2,500 ppm			5,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.6	163	15.2	161	236	14.8	157	471
6	18.2	267	17.4	260	167	16.8	253	332
10	16.5	314	16.5	306	135	16.7	300	279
13	16.7	341	17.1	333	129	16.7	326	256
17	16.5	365	15.9	355	112	16.4	346	238
21	16.8	386	17.6	374	117	16.5	362	227
25	16.0	399	16.1	386	104	15.7	376	209
29	16.8	412	16.5	401	103	15.3	384	199
33	16.3	424	16.4	413	99	16.5	401	205
37	16.0	432	16.2	423	96	15.1	412	183
41	14.5	442	15.2	431	88	15.3	424	180
45	15.8	440	16.0	432	93	16.3	420	194
49	15.9	452	15.9	438	91	16.3	430	189
53	15.7	454	15.6	444	88	15.9	438	182
57	16.5	458	15.9	454	88	15.0	446	169
61	15.8	461	16.0	452	88	16.1	438	184
65	16.1	463	15.6	449	87	15.7	445	176
73	15.5	455	15.2	446	85	14.9	435	171
77	15.1	450	14.7	443	83	15.1	431	175
81	14.4	444	14.9	442	84	13.6	428	159
85	14.2	443	14.4	442	82	12.5	428	146
89	13.2	440	13.8	440	79	11.7	418	140
93	13.5	435	13.2	429	77	12.6	412	152
97	13.8	432	13.6	433	78	12.4	403	154
101	12.6	432	12.6	426	74	13.5	408	166
Mean for weeks								
1-13	16.7	271	16.6	265	167	16.3	259	335
14-52	16.1	417	16.2	406	100	15.9	395	203
53-101	14.7	447	14.6	442	83	14.1	427	165

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol (continued)

Week	0 ppm		10,000 ppm			20,000 ppm		
	Feed (g/day)	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.6	163	14.7	152	965	12.6	134	1,881
6	18.2	267	16.2	236	685	14.7	197	1,489
10	16.5	314	16.1	273	590	14.1	222	1,267
13	16.7	341	16.4	298	548	16.0	245	1,308
17	16.5	365	15.3	319	481	15.2	292	1,041
21	16.8	386	16.0	340	471	16.4	323	1,013
25	16.0	399	15.8	355	445	15.3	347	885
29	16.8	412	15.8	367	429	14.7	366	806
33	16.3	424	15.9	377	422	15.5	382	810
37	16.0	432	15.7	388	404	14.9	399	750
41	14.5	442	14.7	396	372	14.6	410	713
45	15.8	440	15.7	395	398	15.9	410	778
49	15.9	452	16.7	401	416	15.6	419	744
53	15.7	454	15.6	414	377	15.3	430	713
57	16.5	458	15.8	418	379	15.0	431	697
61	15.8	461	16.3	415	393	15.6	422	741
65	16.1	463	15.6	414	377	16.3	429	758
73	15.5	455	14.8	406	365	13.3	423	630
77	15.1	450	14.2	416	341	15.2	424	718
81	14.4	444	11.4	407	281	13.3	414	641
85	14.2	443	12.6	402	315	13.1	410	637
89	13.2	440	12.9	394	327	11.8	409	577
93	13.5	435	13.5	388	348	8.9	374	478
97	13.8	432	12.4	384	323	15.2	402	755
101	12.6	432	12.2	369	331			
Mean for weeks								
1-13	16.7	271	15.8	240	697	14.4	200	1,486
14-52	16.1	417	15.7	371	426	15.4	372	838
53-101	14.7	447	14.0	402	347	13.9	415	668

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

	0 ppm		2,500 ppm			5,000 ppm			10,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	11.6	130	11.5	127	226	11.4	126	452	11.5	127	909
6	11.6	168	11.9	165	180	11.8	165	357	11.3	159	707
10	10.8	185	10.8	180	149	10.7	178	301	10.7	172	621
13	10.1	191	10.2	187	136	10.3	186	277	10.0	180	558
17	10.6	201	10.3	198	130	10.2	193	265	9.9	186	532
21	9.9	206	10.4	203	127	10.1	198	254	10.1	192	524
25	9.7	212	10.0	209	120	9.8	203	241	9.6	199	483
29	10.2	220	10.2	214	119	9.6	211	229	9.7	205	475
33	10.2	224	10.5	220	119	10.4	214	244	10.1	209	485
37	9.7	231	9.9	229	108	9.8	221	220	9.9	215	460
41	9.7	238	9.8	234	105	9.7	237	206	9.8	224	439
45	10.6	246	11.2	240	116	10.9	234	233	10.9	228	479
49	10.8	258	11.0	254	108	11.1	247	224	9.4	239	395
53	11.1	268	11.8	265	111	11.0	257	213	11.2	247	454
57	11.7	282	11.5	277	103	11.1	270	206	11.7	259	451
61	11.6	289	12.0	284	106	11.5	275	210	11.4	262	435
65	12.8	299	12.1	293	103	11.5	283	203	11.1	269	414
73	11.8	308	11.9	300	100	11.5	291	197	11.3	277	410
77	11.7	314	12.0	305	98	11.6	295	196	11.7	284	411
81	10.5	313	11.2	308	91	11.0	299	183	10.3	291	356
85	11.0	312	11.3	307	92	10.6	296	179	10.7	286	376
89	10.6	315	10.8	314	86	10.2	305	167	10.0	293	341
93	10.9	319	11.6	318	91	10.8	311	173	10.4	297	351
97	11.4	326	10.2	325	79	11.8	323	183	11.1	301	367
101	10.9	330	11.5	327	88	11.2	322	174	12.2	307	396
Mean for weeks											
1-13	11.0	168	11.1	165	173	11.0	164	347	10.9	159	699
14-52	10.2	226	10.4	222	117	10.2	218	235	9.9	211	475
53-101	11.3	306	11.5	302	96	11.1	294	190	11.1	281	397

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	24.9	4.6	24.9	57	4.4	24.8	111	4.6	24.7	230
6	4.9	28.8	4.9	28.7	53	5.0	28.3	109	4.9	28.2	218
10	4.7	31.8	5.0	32.2	48	4.7	31.4	94	4.8	31.1	193
13	4.6	33.5	4.7	33.7	43	4.7	32.9	90	4.7	32.6	180
17	4.7	34.8	5.0	35.0	45	5.1	34.0	94	4.9	33.8	182
21	4.4	36.9	4.8	37.7	40	4.8	36.7	81	4.8	36.3	164
25	4.3	38.8	4.6	39.6	36	4.4	38.5	72	4.6	37.8	150
29	4.5	40.7	4.6	41.3	35	4.6	40.1	72	4.7	39.7	148
33	4.7	42.2	4.7	43.5	34	4.9	41.7	73	5.0	41.2	153
37	4.8	43.6	4.7	44.4	33	4.9	43.2	70	4.8	42.4	143
41	4.4	44.5	4.7	44.8	32	4.6	44.1	65	4.8	43.3	140
45	4.2	46.4	4.4	46.8	29	4.5	45.9	61	4.6	45.1	127
49	4.4	46.7	4.7	46.9	31	4.5	46.5	61	4.4	45.2	120
53	4.4	47.3	4.7	47.6	31	4.7	46.9	62	4.5	46.1	123
57	4.5	48.2	4.7	49.1	30	4.6	48.5	59	4.8	47.5	125
61	4.7	48.8	4.7	49.4	30	4.7	49.1	60	4.5	48.1	118
65	4.7	49.0	4.9	49.2	31	4.8	49.4	61	4.8	48.0	126
69	4.5	47.6	4.7	48.9	30	4.6	48.5	60	4.4	47.9	116
73	4.3	48.4	4.7	48.7	30	4.6	47.8	60	4.5	47.6	119
77	4.5	48.1	4.7	49.1	30	4.6	48.5	60	4.5	47.7	119
81	4.4	47.3	4.6	47.8	30	4.3	47.1	57	4.4	46.0	120
85	4.7	48.8	4.9	48.7	32	4.8	48.5	61	4.9	46.2	133
90	4.2	49.4	4.5	49.3	29	4.5	47.9	58	4.3	47.2	115
93	4.1	49.7	4.5	49.3	28	4.4	48.6	56	4.4	46.9	117
97	4.5	49.8	4.7	48.9	30	4.5	48.6	58	4.6	46.6	124
101	4.4	48.7	4.5	48.3	29	4.5	47.6	59	4.4	44.6	122
Mean for weeks											
1-13	4.7	29.7	4.8	29.9	50	4.7	29.3	101	4.7	29.2	205
14-52	4.5	41.6	4.7	42.2	35	4.7	41.2	72	4.7	40.5	148
53-101	4.4	48.5	4.7	48.8	30	4.6	48.2	59	4.6	47.0	121

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of 2,2-Bis(bromomethyl)-1,3-propanediol

Week	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.4	20.5	4.5	20.7	68	4.6	20.3	143	4.4	20.2	272
6	4.9	24.3	5.1	24.1	66	5.4	23.7	141	5.3	23.5	279
10	5.1	26.5	5.2	26.9	61	5.3	26.5	124	5.5	26.0	267
13	5.3	28.0	5.0	28.8	54	5.2	28.0	116	5.3	27.5	241
17	4.9	30.1	5.3	30.7	54	5.4	29.9	112	5.4	29.1	233
21	5.0	31.6	5.2	32.6	50	5.4	32.5	104	5.4	30.9	217
25	5.0	34.5	5.1	35.8	44	5.2	35.6	91	5.2	33.7	191
29	4.8	36.2	5.1	37.8	42	4.9	37.5	81	5.3	35.5	185
33	5.3	37.4	5.5	39.4	43	5.5	39.0	88	5.8	37.0	195
37	5.5	39.3	5.6	41.5	42	5.6	41.1	86	6.0	38.9	192
41	4.9	40.7	5.2	43.2	37	5.2	43.0	76	5.5	40.7	168
45	5.1	42.8	4.8	44.8	33	4.9	44.5	69	5.4	43.0	157
49	4.8	44.8	4.9	46.3	33	5.1	45.4	71	4.8	44.0	137
53	5.0	46.0	5.0	48.1	32	5.2	47.2	69	4.9	45.8	135
57	5.0	48.0	5.0	50.3	31	5.0	48.6	65	5.2	47.9	137
61	5.1	49.6	5.1	51.4	31	5.0	50.4	63	5.1	49.6	128
65	5.0	50.2	5.1	52.1	30	5.5	51.7	67	5.6	49.5	142
69	4.5	50.0	5.0	51.6	30	5.2	50.9	64	5.1	49.0	129
73	4.7	50.8	5.1	51.1	31	5.1	51.2	62	5.0	49.3	127
77	4.7	50.9	5.1	51.1	31	4.8	50.5	60	5.2	49.1	133
81	4.7	50.2	5.0	50.0	31	4.7	50.2	59	4.8	49.1	121
85	5.3	52.4	5.3	51.1	33	5.5	51.2	67	6.1	50.3	151
89	4.5	53.6	4.6	52.4	28	4.4	52.0	53	4.9	50.7	120
93	4.4	53.9	4.9	52.6	29	4.6	51.9	55	4.9	49.7	124
97	4.8	54.5	4.9	53.7	29	4.9	51.9	60	5.2	49.4	133
101	4.7	52.4	4.6	52.3	28	4.7	50.8	57	4.9	47.6	128
Mean for weeks											
1-13	4.9	24.8	5.0	25.1	62	5.1	24.6	131	5.1	24.3	265
14-52	5.0	37.5	5.2	39.1	42	5.2	38.7	86	5.4	37.0	186
53-101	4.8	51.0	5.0	51.4	30	5.0	50.6	62	5.1	49.0	131

[a] Grams of feed consumed per animal per day
[b] Milligrams of 2,2-bis(bromomethyl)-1,3-propanediol consumed per kilogram body weight per day

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

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.44 ± 0.83	21.30 — 25.20	25
Crude fat (% by weight)	5.24 ± 0.22	4.80 — 5.80	25
Crude fiber (% by weight)	3.60 ± 0.55	2.60 — 4.80	25
Ash (% by weight)	6.55 ± 0.20	6.12 — 7.10	25
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 — 1.390	10
Cystine	0.306 ± 0.075	0.181 — 0.400	10
Glycine	1.160 ± 0.050	1.060 — 1.220	10
Histidine	0.580 ± 0.024	0.531 — 0.608	10
Isoleucine	0.917 ± 0.034	0.867 — 0.965	10
Leucine	1.972 ± 0.052	1.850 — 2.040	10
Lysine	1.273 ± 0.051	1.200 — 1.370	10
Methionine	0.437 ± 0.115	0.306 — 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 — 1.110	10
Threonine	0.896 ± 0.055	0.824 — 0.985	10
Tryptophan	0.223 ± 0.160	0.107 — 0.671	10
Tyrosine	0.677 ± 0.105	0.564 — 0.794	10
Valine	1.089 ± 0.057	0.962 — 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 — 2.570	9
Linolenic	0.277 ± 0.036	0.210 — 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,664 ± 1,277	4,273 — 9,190	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 — 48.9	9
Thiamine (ppm)	19.76 ± 2.65	15.0 — 28.0	25
Riboflavin (ppm)	7.92 ± 0.93	6.10 — 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 — 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 — 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 — 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 — 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 — 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 — 65.0	10
Choline (ppm)	3,068 ± 314	2,400 — 3,430	9
Minerals			
Calcium (%)	1.22 ± 0.11	0.90 — 1.55	25
Phosphorus (%)	0.95 ± 0.04	0.88 — 1.03	25
Potassium (%)	0.887 ± 0.067	0.772 — 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 — 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 — 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 — 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 — 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 — 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 — 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 — 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 — 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 — 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 — 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 — 1.150	6

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.30 ± 0.16	0.06 — 0.60	25
Cadmium (ppm)	0.08 ± 0.02	0.05 — 0.12	25
Lead (ppm)	0.27 ± 0.18	0.10 — 0.90	25
Mercury (ppm)	0.03 ± 0.02	0.05 — 0.08	25
Selenium (ppm)	0.34 ± 0.08	0.15 — 0.52	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)[c]	15.22 ± 4.43	5.90 — 22.00	25
Nitrite nitrogen (ppm)[c]	0.20 ± 0.14	<0.10 — 0.60	25
BHA (ppm)[d]	1.54 ± 0.88	<1.00 — 4.00	25
BHT (ppm)[d]	1.46 ± 1.25	<1.00 — 7.00	25
Aerobic plate count (CFU/g)	95,068 ± 78,430	4,700 — 380,000	25
Coliform (MPN/g)	28.84 ± 31.01	<3.00 — 93.00	25
Escherichia coli (MPN/g)	3.32 ± 1.21	<3.00 — 9.00	25
Salmonella (MPN/g)	Negative		
Total nitrosoamines (ppb)[e]	7.30 ± 2.45	2.00 — 13.70	25
N-Nitrosodimethylamine (ppb)[e]	5.38 ± 2.06	1.00 — 11.00	25
N-Nitrosopyrrolidine (ppb)[e]	1.92 ± 1.04	1.00 — 4.30	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.27 ± 0.29	0.05 — 1.29	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] CFU = colony forming units, MPN = most probable number, BHC is hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected, allowed to clot and the serum separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
13-Week Study	
ELISA	
CARB (cilia-associated respiratory bacillus)	Study termination
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
RCV/SDA	18 months and study termination
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

MICE

13-Week Study

Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	18 months
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
MVM	6 months
Mouse adenoma virus	6 and 18 months, study termination
MHV	6, 12, 18, 21, and 22 months, study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, 18, 21, and 22 months, study termination
Sendai	6, 12, 18, 21, and 22 months, study termination
Immunofluorescence Assay	
EDIM	6 and 12 months, study termination
GDVII	18 months
LCM	18 months and study termination
MVM	12 months
Mouse adenoma virus	12 and 18 months
MHV	18 months
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	18 months and study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of 2,2-Bis(bromomethyl)-1,3-propanediol

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/1[a]	None positive
2-Year Studies		
Rats		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
Study termination	2/9	*M. arthritidis*[b]
Mice		
6 Months	0/8	None positive
12 Months	0/10	None positive
18 Months	0/9	None positive
21 Months	2/10	MHV
22 Months	0/10	None positive
Study termination	4/4	MHV
	10/10	MHV
	4/5	MHV

[a] Six samples were received at Microbiological Associates, Inc.; however, on the day they were to be tested, five vials were found to be empty.

[b] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may be due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive and there were no clinical signs or histopathologic changes of *M. arthritidis* infection in rats with positive titers. Accordingly, *M. arthritidis*-positive titers were considered to be false positives.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD E1-02
Research Triangle Park, NC 27709

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Penalty for Private Use - $300

NIH Publication No. 96-3368
May 1996