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TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIBROMOMETHANE (BROMOFORM)

(CAS NO. 75-25-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIBROMOMETHANE (BROMOFORM)

(CAS NO. 75-25-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

Ronald L. Melnick, Ph.D., Study Scientist

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

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Public Health Service
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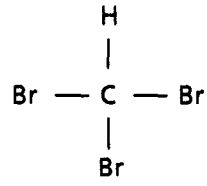

TRIBROMOMETHANE

(BROMOFORM)

CAS No. 75-25-2

$CHBr_3$ Molecular weight: 252.8

ABSTRACT

Tribromomethane, a chemical intermediate and solvent, has been identified as a drinking water contaminant resulting from water chlorination. Toxicology and carcinogenesis studies were conducted by administering tribromomethane (95%-97% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex once or for 14 days, 13 weeks, or 2 years.

Single-Administration, Fourteen-Day, and Thirteen-Week Studies: All rats that received 2,000 mg/kg and 3/5 males and 3/5 females that received 1,000 mg/kg tribromomethane died before the end of the single-administration studies. All mice that received 2,000 mg/kg, 4/5 males and 2/5 females that received 1,000 mg/kg, and 1/5 males that received 500 mg/kg died before the end of the studies. Shallow breathing was observed for rats and male mice that received 1,000 or 2,000 mg/kg tribromomethane.

In the 14-day studies, all rats that received 600 or 800 mg/kg and 1/5 males that received 400 mg/kg tribromomethane died before the end of the studies. The final mean body weight of male rats that received 400 mg/kg was 14% lower than that of vehicle controls. One of five male mice that received 600 mg/kg and 1/5 female mice that received 800 mg/kg died before the end of the studies. Final mean body weights of dosed and vehicle control mice were comparable.

None of the rats died before the end of the 13-week studies (doses ranged from 12 to 200 mg/kg). Final mean body weights were comparable for dosed and vehicle control rats. All male rats that received 100 or 200 mg/kg tribromomethane and all female rats that received 200 mg/kg were lethargic. The incidences of cytoplasmic vacuolization of hepatocytes in dosed male rats were slightly increased compared with that in vehicle controls. The severity of this lesion was increased in the 200 mg/kg group. One of 10 female mice that received 100 mg/kg tribromomethane died before the end of the 13-week studies. The final mean body weight of mice that received 400 mg/kg was 8% lower than that of vehicle controls for males and was comparable to that of vehicle controls for females. Cytoplasmic vacuolization of hepatocytes was observed in the liver of 5/10 male mice that received 200 mg/kg and in 8/10 male mice that received 400 mg/kg tribromomethane.

Based on these results, 2-year studies of tribromomethane were conducted by administering 0, 100, or 200 mg/kg tribromomethane in corn oil by gavage, 5 days per week for 103 weeks, to groups of 50 F344/N rats of each sex and 50 female B6C3F$_1$ mice. Male B6C3F$_1$ mice were administered 0, 50, or 100 mg/kg tribromomethane on the same schedule.

Body Weights and Survival in the Two-Year Studies: Mean body weights of high dose male and female rats were 10%-28% lower than those of vehicle controls throughout the second year of the studies. Survival of the high dose group of male rats was significantly lower than that of the vehicle controls after week 91; no significant differences in survival were observed between any groups of female rats (male: vehicle control, 34/50; low dose, 30/50; high dose, 11/50; female: 34/50; 28/50; 28/50). Reduced survival for male rats given 200 mg/kg tribromomethane lowered the sensitivity of this group to detect a carcinogenic response. Mean body weights of dosed and vehicle control male mice were comparable throughout the study. Mean body weights of dosed female mice were 5%-16% lower than those of vehicle controls from week 28 to the end of the study. No significant differences in survival were observed between any groups of male mice; the survival of both dosed groups of female mice was significantly lower than that of the vehicle controls after week 77 (male: 41/50; 37/50; 36/50; female: 25/49; 15/50; 20/50). Reduced survival in all groups of female mice was partly due to a utero-ovarian infection; nonetheless, survival of all groups of female mice was at least 50% by week 92.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Uncommon adenomatous polyps or adenocarcinomas (combined) of the large intestine (colon or rectum) were induced in three male rats (vehicle control, 0/50; low dose, 0/50; high dose, 3/50) and in nine female rats (0/50; 1/50; 8/50); the historical incidence of neoplasms of the large intestine is less than 0.2% in approximately 2,000 corn oil vehicle control male F344/N rats, and none has been observed in approximately 2,000 corn oil vehicle control female F344/N rats. Three of the neoplasms of the large intestine (one in the high dose male rats and two in the high dose female rats) were adenocarcinomas.

Focal or diffuse fatty change of the liver was observed at increased incidences in dosed rats (male: 23/50; 49/50; 50/50; female: 19/50; 39/49; 46/50). Active chronic inflammation was observed at increased incidences in dosed male and high dose female rats (male: 0/50; 29/50; 23/50; female: 9/50; 8/49; 27/50). The incidence of necrosis of the liver was increased in high dose male rats (7/50; 3/50; 20/50) and decreased in dosed females (11/50; 3/49; 2/50). Mixed cell focus was observed at increased incidences in dosed female rats (8/50; 25/49; 28/50).

Other nonneoplastic lesions observed at increased incidences in dosed rats included chronic active inflammation and squamous metaplasia of the ducts of the salivary gland (squamous metaplasia--male: 0/50; 15/50; 31/48; female: 0/49; 10/49; 16/50; chronic active inflammation--male: 0/50; 16/50; 25/48; female: 0/49; 9/49; 18/50), squamous metaplasia of the prostate gland (2/49; 6/46; 12/50), ulcers of the forestomach (male: 1/49; 5/50; 10/50), and chronic active inflammation of the lung (male: 1/50; 7/50; 15/50). Pigmentation of the spleen was also observed at an increased incidence in high dose female rats. The salivary gland and lung lesions were characteristic of infection by rat coronavirus, a virus to which a positive serologic reaction was observed early in the studies.

The incidence of follicular cell hyperplasia of the thyroid gland was increased in high dose female mice (5/49; 4/49; 19/47), and fatty change of the liver was increased in both dosed groups of female mice (1/49; 9/50; 24/50). No chemically related adverse effects were observed in male mice.

Neoplastic lesions that occurred at lower incidences in dosed animals compared with those in vehicle controls included preputial gland neoplasms in male rats (10/41; 5/38; 1/34), uterine stromal polyps in female rats (10/49; 9/50; 2/50), anterior pituitary gland adenomas in male and female rats (male: 12/50; 12/48; 2/45; female: 29/48; 12/46; 16/48), mammary gland fibroadenomas in female rats (22/50; 17/50; 6/50), and alveolar/bronchiolar neoplasms in male mice (11/50; 7/50; 2/49). Other than concomitant decreases in body weights, no other reasons are obvious to correlate these decreases with chemical administration.

Genetic Toxicology: Tribromomethane exhibited equivocal mutagenicity in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation and in strains TA97 and TA98 when exposure occurred in the presence of hamster S9; tribromomethane produced no increases in revertant colonies in TA1535 or TA1537 with or without exogenous metabolic activation. Tribromomethane induced trifluorothymidine (Tft) resistance in mouse L5178Y cells with and without metabolic activation. When tested in cultured Chinese hamster ovary (CHO) cells for cytogenetic effects, tribromomethane produced an increase in both sister chromatid exchanges (SCEs) and chromosomal aberrations in the absence, but not in the presence, of exogenous metabolic activation. Tribromomethane caused sex-linked recessive lethal mutations in Drosophila when administered to adult males by feeding; no induction of mutations was observed when tribromomethane was administered by abdominal injection. Results of tests for reciprocal translocations in adult male Drosophila exposed to tribromomethane by feeding were negative. In vivo tests for cytogenetic effects in bone marrow cells of male $B6C3F_1$ mice demonstrated that intraperitoneal injection of tribromomethane induced an increase in SCEs but no increase in chromosomal aberrations. Intraperitoneal injection of tribromomethane also induced an increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow of $B6C3F_1$ mice.

Audit: The data, documents, and pathology materials from the 2-year studies of tribromomethane have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of tribromomethane for male F344/N rats and *clear evidence of carcinogenic activity* for female F344/N rats, based on increased incidences of uncommon neoplasms of the large intestine. Reduced survival for male rats given 200 mg/kg tribromomethane lowered the sensitivity of this group to detect a carcinogenic response. Chemically related nonneoplastic lesions included fatty change and active chronic inflammation of the liver in male and female rats, minimal necrosis of the liver in male rats, and mixed cell foci of the liver in female rats. There was *no evidence of carcinogenic activity* for male $B6C3F_1$ mice given 50 or 100 mg/kg tribromomethane or for female $B6C3F_1$ mice given 100 or 200 mg/kg; male mice might have been able to tolerate a higher dose. Survival of the female mice was reduced, partly due to a utero-ovarian infection.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF TRIBROMOMETHANE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 100, or 200 mg/kg tribromomethane in corn oil, 5 d/wk	0, 100, or 200 mg/kg tribromomethane in corn oil, 5 d/wk	0, 50, or 100 mg/kg tribromomethane in corn oil, 5 d/wk	0, 100, or 200 mg/kg tribromomethane in corn oil, 5 d/wk
Body weights in the 2-year study			
Reduced in dosed groups	Reduced in high dose group	Similar in all groups	Reduced in dosed groups
Survival rates in the 2-year study			
34/50; 30/50; 11/50	34/50; 28/50; 28/50	41/50; 37/50; 36/50	25/49; 15/50; 20/50
Nonneoplastic effects			
Liver: fatty change, inflammation, and minimal necrosis	Liver: fatty change, inflammation, and mixed cell foci	None	Liver: fatty change; thyroid gland: follicular cell hyperplasia
Neoplastic effects			
Adenomatous polyps or adenocarcinomas (combined) in the large intestine: 0/50; 0/50; 3/50	Adenomatous polyps or adenocarcinomas (combined) in the large intestine: 0/50; 1/50; 8/50	None	None
Level of evidence of carcinogenic activity			
Some evidence	Clear evidence	No evidence	No evidence
Other considerations			
Reduced survival in high dose group			Utero-ovarian infections and reduced survival in all groups

Genetic toxicology

		CHO Cells in Vitro		Drosophila		In Vivo Cytogenetics	
Salmonella (gene mutation)	Mouse L5178Y (Tft resistance)	SCE	Aberration	Sex-Linked Rec. Lethals	Reciprocal Translocation	SCE/Aberration (bone marrow)	Micronuclei
Equivocal with and without S9	Positive with and without S9	Weakly positive without S9; negative with S9	Weakly positive without S9; negative with S9	Positive	Negative	Positive/negative	Positive

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 because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports 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 quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of 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 chemically 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 chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically 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. This 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:

- The 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 incidences 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);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tribromomethane is based on 13-week studies that began in March 1980 and ended in June 1980 and on 2-year studies that began in February 1981 and ended in March 1983 at EG&G Mason Research Institute (Worcester, Massachusetts).

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

Ronald Melnick, Ph.D., Study Scientist

John Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.

(Discipline Leaders and Principal Contributors)

Jack Bishop, Ph.D.
Douglas W. Bristol, Ph.D.
R. Chhabra, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
M. Vernon, Ph.D.
Douglas Walters, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 5/13/86)

Gary Boorman, D.V.M., Ph.D. (Chair) (NTP)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
William Macklin, D.V.M., Ph.D. (Burroughs Wellcome Laboratories)
Kunitoshi Mitsumori, D.V.M., Ph.D. (NTP)
A.S. Krishna Murthy, Ph.D. (EG&G Mason Research Institute)
Gary Riley, M.V.Sc., Ph.D. (Experimental Pathology Laboratories, Inc.)

(Evaluated Slides and Prepared Pathology Report for Mice on 5/13/86)

Michael Elwell, D.V.M., Ph.D. (Chair) (NTP)
Gary Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
William Macklin, D.V.M., Ph.D. (Burroughs Wellcome Laboratories)
Kunitoshi Mitsumori, D.V.M., Ph.D. (NTP)
A.S. Krishna Murthy, Ph.D. (EG&G Mason Research Institute)
Gary Riley, M.V.Sc., Ph.D. (Experimental Pathology Laboratories, Inc.)

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

Herman Lilja, Ph.D.
A.S. Krishna Murthy, Ph.D.
Miasnig Hagopian, Ph.D.

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Provided Pathology Quality Assurance)

J. Gauchat
Roger Brown, D.V.M.
G. Riley, M.V.Sc., Ph.D.

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

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.
Naomi Levy, B.A.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on tribromomethane on April 18, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D. (Chair)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

Michael A. Gallo, Ph.D.
Associate Professor, Director of Toxicology
Department of Environmental and Community Medicine, UMDNJ - Rutgers Medical School
Piscataway, New Jersey

Frederica Perera, Dr. P.H. (Principal Reviewer) Division of Environmental Sciences, School of Public Health
Columbia University
New York, New York

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D.
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderley Park, England

Charles C. Capen, D.V.M., Ph.D. (Principal Reviewer) Department of Veterinary Pathobiology, Ohio State University
Columbus, Ohio

Vernon M. Chinchilli, Ph.D.
Department of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

Kim Hooper, Ph.D. (Principal Reviewer)
Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

Donald H. Hughes, Ph.D.
Scientific Coordinator, Regulatory Services Division, The Procter and Gamble Company
Cincinnati, Ohio

William Lijinsky, Ph.D.
Director, Chemical Carcinogenesis
Frederick Cancer Research Facility
Frederick, Maryland

Franklin E. Mirer, Ph.D.*
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Andrew Sivak, Ph.D.
Vice President, Biomedical Science
Arthur D. Little, Inc.
Cambridge, Massachusetts

*Unable to attend

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

On April 18, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of tribromomethane received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.

Dr. R.L. Melnick, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats, clear evidence of carcinogenic activity for female rats, no evidence of carcinogenic activity for male or female mice).

Dr. Hooper, a principal reviewer, agreed with the conclusions. He commented on the negative trends for neoplasia at several sites in male rats (mononuclear cell leukemia, preputial gland adenomas/carcinomas) and in female rats (mammary gland fibroadenomas, anterior pituitary gland adenomas, endometrial stromal polyps).

Dr. Capen, the second principal reviewer, agreed with the conclusions. He noted the fairly striking increased incidence of follicular cell hyperplasia in the thyroid gland of high dose female mice and wondered about the possible mechanism.

Dr. Perera, the third principal reviewer, agreed with the conclusions for male and female rats and male mice. She said that the significantly reduced survival in exposed female mice suggested a change to inadequate study of carcinogenic activity. Dr. Melnick responded that survival in all female mice groups was greater than 50% at 92 weeks. Because the liver was the only site of significant neoplasia caused by other trihalomethanes in female mice, he thought that the survival in the present study was adequate to have detected such an effect. In other discussion, Dr. Sivak commented that since the primary rationale for the studies was based on the presence of tribromomethane in drinking water, inclusion of a comparison between drinking water levels and doses used would be helpful to the reader [see page 12].

Dr. Capen moved that the Technical Report on tribromomethane be accepted with revisons as discussed and with the conclusions as written: for male rats, some evidence of carcinogenic activity; for female rats, clear evidence of carcinogenic activity; and for male and female mice, no evidence of carcinogenic activity. Dr. Hooper seconded the motion, which was approved unanimously with 10 votes.

I. INTRODUCTION

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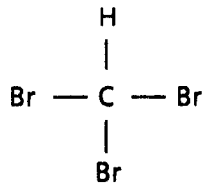


TRIBROMOMETHANE

(BROMOFORM)

CAS No. 75-25-2

$CHBr_3$ Molecular weight: 252.8

Physical and Chemical Properties, Use, Production, and Exposure

Tribromomethane is a colorless liquid (melting point: 6°-7° C; boiling point: 149.5° C at 760 mm mercury; specific gravity: 2.890; vapor pressure: 5.6 mm mercury at 25° C; percent in saturated air: 0.7% at 25° C) that is miscible with ethanol, ether, and benzene and slightly soluble in water (0.30% at 30° C) (Torkelson and Rowe, 1981; Merck, 1983). The TSCA Initial Inventory reported that domestic production of tribromomethane was 50,000-500,000 kg in 1977 (USEPA, 1987). The U.S. International Trade Commission did not report the volume of domestic production of tribromomethane for the years 1981-85 (USITC, 1986). Current production data for tribromomethane are not available.

Tribromomethane has been used as a chemical intermediate (e.g., synthesis of carbon tetrabromide); as a solvent for waxes, greases, and oils; as a high density liquid for petrographic analysis; and formerly as a sedative and an antitussive.

The major source of human exposure to trihalomethanes is drinking water (Cotruvo, 1981). Tribromomethane was detected in 27/80 water supplies in a national survey conducted by the U.S. Environmental Protection Agency (EPA) (Symons et al., 1975); the mean concentration of tribromomethane was 6.5 µg/liter, and the concentration range was 0.8-92 µg/liter. In a followup survey, tribromomethane was detected in 38/113 public water supplies; the mean concentration of tribromomethane in positive samples was 12 µg/liter (Brass et al., 1977). Tribromomethane was detected in 22% of groundwater samples and 33% of surface water samples obtained from more than 1,000 wells and 600 surface water sites throughout New Jersey (Page, 1981).

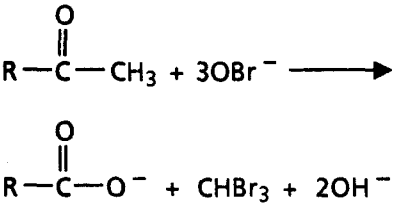
Of synthetic organic chemicals detected in drinking water, the trihalomethanes are found most frequently and generally at the highest concentrations. Trihalomethanes are formed as by-products of water chlorination. In response to the discovery of trihalomethanes in drinking water, the EPA promulgated regulations limiting the maximum permissible contaminant level for total trihalomethanes in drinking water to 100 µg/liter (Fed. Regist., 1979). Thus, a 70-kg adult human consuming 2 liters per day of water containing 100 µg of trihalomethane per liter would receive a daily dose of trihalomethane equivalent to 2.9 µg/kg. The American Conference of Governmental Industrial Hygienists recommends a threshold limit value of 0.5 ppm (approximately 5 mg/m^3) for tribromomethane (ACGIH, 1986). Approximately 1,500 workers are potentially exposed to tribromomethane, as estimated from data compiled from the National Occupational Exposure Survey (NIOSH, unpublished data).

Tribromomethane can be produced during chlorination of surface water if bromide and organic carbon precursors are present (Williams, 1985). Bromide is oxidized to hypobromite by hypochlorous acid; the latter compound is formed when chlorine gas is dissolved in water:

$$Cl_2 + H_2O \rightleftharpoons H^+ + Cl^- + HOCl$$

$$HOCl + Br^- \longrightarrow HOBr + Cl^-$$

If sodium or calcium hypochlorite is used as the source of chlorine, the hypochlorite ion (OCl^-) rapidly establishes equilibrium with hypochlorous acid. Hypobromite is capable of undergoing the haloform type reaction with organic humic material or other organic precursors to produce tribromomethane (Bunn et al., 1975):



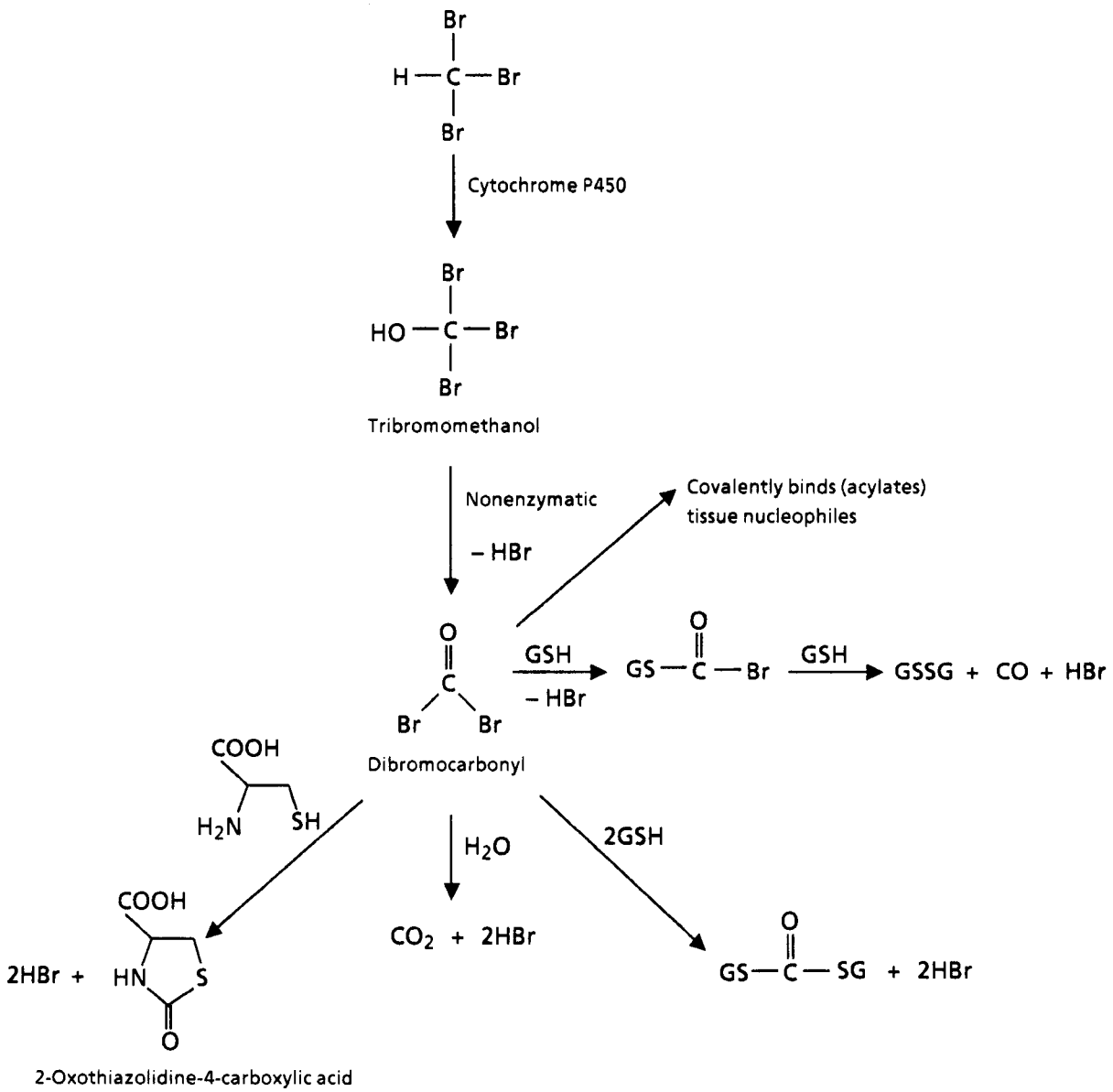
The rate of formation of trihalomethanes is dependent on the chlorine concentration, total organic carbon, pH, temperature, and bromide concentration (Umphres et al., 1981; Williams, 1985).

Trihalomethanes also are produced in cooling water used by the electric power industry when chlorine is added as a biofouling control agent (Smith et al., 1983). Tribromomethane is the major halogenated organic compound produced as a result of chlorination of seawater in ocean thermal energy conversion processes (Hartwig and Valentine, 1983). Tribromomethane also has been found in swimming pools (Beech et al., 1980).

Metabolism

Stevens and Anders (1981) proposed the reaction scheme presented on the following page for the metabolism of haloforms (shown here for tribromomethane).

Studies on haloform metabolism were initiated because administration of haloforms to rats results in elevated blood carbon monoxide and carboxyhemoglobin concentrations. The metabolism of tribromomethane to carbon monoxide in rat liver is catalyzed by a microsomal cytochrome P450-dependent mono-oxygenase requiring NADPH and molecular oxygen for maximal activity; sulfhydryl compounds (e.g., glutathione) increase the rate of formation of carbon monoxide from tribromomethane (Ahmed et al., 1977). The glutathione-dependent production of carbon monoxide constitutes a detoxification pathway for dihalocarbonyls formed during biotransformation of haloforms; however, the product of this pathway (carbon monoxide) is also toxic (Stevens and Anders, 1981). Pretreatment of rats with phenobarbital or 3-methylcholanthrene increased the rate of in vitro conversion of tribromomethane to carbon monoxide (Ahmed et al., 1977), whereas only phenobarbital pretreatment led to increased blood levels of carbon monoxide after administration of tribromomethane or chloroform (trichloromethane) to rats (Anders et al., 1978; Pohl et al., 1980). Tribromomethane produced a type I binding spectrum with oxidized cytochrome P450, and the rate of biotransformation of tribromomethane to carbon monoxide was inhibited by SKF 525-A, a mixed-function oxidase inhibitor (Ahmed et al., 1977). Compared with tribromomethane, $CDBr_3$ (deuterium-labeled tribromomethane) was less hepatotoxic and resulted in lower levels of carbon monoxide in blood in rats (Anders et al., 1978; Pohl et al., 1980). The deuterium effect indicates that the C-H bond cleavage is the rate-limiting step in the biotransformation of tribromomethane to hepatotoxic metabolites. Dibromocarbonyl (the bromine analog of phosgene) has been suggested to be an intermediate in the metabolism of tribromomethane, since 2-oxothiazolidine-4-carboxylic acid was formed when hepatic microsomes were incubated with tribromomethane plus cysteine (Stevens and Anders, 1979). This reactive intermediate may be responsible for tribromomethane-induced hepatotoxicity (see Animal Toxicity, p. 15). Cysteine treatment of rats, before chloroform administration, decreased blood carbon monoxide levels and protected against chloroform-induced hepatotoxicity (Docks and Krishna, 1976).



Dibromocarbonyl also may serve as the precursor for the metabolism of tribromomethane to carbon dioxide (see reaction scheme, above). Depletion of glutathione by haloforms may also occur by reaction of the dihalocarbonyl with glutathione, forming *S,S'*-diglutathionyl carbonate. Liver glutathione levels were decreased in phenobarbital-pretreated Sprague Dawley rats that were subsequently dosed with chloroform (Docks and Krishna, 1976); tribromomethane was less effective than chloroform in causing glutathione depletion.

The hepatotoxicity of tribromomethane and other haloforms appears to be related to their metabolism. Pretreatment of rats with phenobarbital produces parallel changes in the metabolism and hepatotoxicity of chloroform and tribromomethane, whereas sulfhydryl compounds provide a detoxification pathway for the haloforms. Tomasi et al. (1985) suggested that trihalomethanes might also undergo reductive metabolism mediated by cytochrome P450, since free radical intermediates were detected by an electron spin resonance (ESR) spin-trapping

technique (spin trap: phenyl-*t*-butyl nitrone) in isolated hepatocytes incubated under nitrogen with several trihalomethanes and in the liver of phenobarbital-induced Wistar rats administered chloroform, tribromomethane, bromodichloromethane, or triiodomethane. In hepatocytes, the intensity of the ESR signal was reduced by exposure to oxygen or by the addition of cytochrome P450 inhibitors (SKF-525A, metyrapone, and carbon monoxide).

Trihalomethanes are rapidly absorbed after oral administration, metabolized primarily to carbon dioxide, and rapidly excreted. More than 92% of a dose of 60 mg/kg of [^{14}C]chloroform was eliminated within 48 hours in expired air, urine, or feces from rats, mice, and squirrel monkeys (Brown et al., 1974). The conversion of the administered dose to [^{14}C]carbon dioxide was about 85% in mice (CBA, CF/LP, and C57 Black strains), 66% in Sprague Dawley rats, and 18% in squirrel monkeys. Variability in the biotransformation and elimination of chloroform in humans was indicated in a study in which 17.8%-66.6% of a 500 mg dose of chloroform was recovered from volunteers over an 8-hour period (Cotruvo, 1981).

Animal Toxicity

Tribromomethane has been considered to be a moderately toxic chemical that can be absorbed through the lungs, gastrointestinal tract, and skin (von Oettingen, 1955). The oral LD_{50} value for tribromomethane is 1,400 and 1,550 mg/kg in male and female ICR Swiss mice (Bowman et al., 1978) and 1,388 and 1,147 mg/kg in male and female Sprague Dawley rats (Chu et al., 1980). Tribromomethane was slightly less acutely toxic than chloroform, bromodichloromethane, or chlorodibromomethane in rats and mice. In male rats, the intraperitoneal LD_{50} value for tribromomethane is 414 µl/kg (1,196 mg/kg) (Agarwal and Mehendale, 1983), and the subcutaneous LD_{50} value in male mice is 7.2 mmol/kg (1,820 mg/kg) (Kutob and Plaa, 1962).

Exposure to tribromomethane vapors may cause irritation to the respiratory tract, lacrimation, and liver damage (von Oettingen, 1955). Death from exposure to tribromomethane at acutely toxic dose levels is most likely due to central nervous system depression. Ataxia, sedation, and anesthesia occur shortly after exposure to tribromomethane at lethal doses (Bowman et al., 1978).

The liver and kidney have been identified as target organs of trihalomethane toxicity in single-exposure or short-term studies. Bowman et al. (1978) reported that the liver of ICR Swiss mice administered trihalomethanes at lethal doses appeared to have fatty infiltration, and the kidneys were pale. Liver changes, described as variation in size of hepatocytes and vesiculation of biliary epithelial nuclei, were observed in female Sprague Dawley rats that survived a single oral dose of tribromomethane (1,071 mg/kg or higher) (Chu et al., 1982a). Kidney changes (bilateral focal interstitial nephritis and fibrosis) were observed in Sprague Dawley rats that survived single oral doses of chloroform, bromodichloromethane, or chlorodibromomethane; however, these changes were not observed in rats exposed to tribromomethane. No pathologic changes were observed in Sprague Dawley rats exposed to tribromomethane at 5, 50, or 500 ppm (equivalent to 0.13, 1.5, and 14 mg per rat per day, respectively) in drinking water for 28 days. Sprague Dawley rats were also exposed to tribromomethane at 5, 50, 500, or 2,500 ppm in drinking water for 90 days (Chu et al., 1982b). The liver lesions were similar to those observed in the single-administration study (Chu et al., 1982a), and the severity was increased in male rats dosed with 2,500 ppm tribromomethane and in female rats dosed with 500 or 2,500 ppm tribromomethane compared with that in vehicle control (1% emulphor) rats.

Condie et al. (1983) administered tribromomethane by gavage to CD-1 mice for 14 days at doses of 0, 72, 145, or 289 mg/kg. Blood urea nitrogen (BUN) and serum creatinine levels were not altered; however, active uptake of *p*-aminohippurate into renal cortical slices was reduced, and serum glutamate-pyruvate transaminase (SGPT) levels were elevated in the high dose animals. Similar effects were observed in animals administered chloroform, bromodichloromethane, or chlorodibromomethane. Histopathologic changes in the kidney (hyperplasia of tubular epithelial cells and hypertrophy and degenerative changes in the glomerular

mesangium) and liver (centrilobular cytoplasmic pallor and slight focal inflammation) were observed in the mid dose and high dose groups.

Administration of tribromomethane in corn oil by intraperitoneal injection to Sprague Dawley rats at doses up to 300 µl/kg (867 mg/kg) did not affect the levels of SGPT, serum glutamic-oxaloacetic transaminase (SGOT), or serum isocitrate dehydrogenase 24 hours after administration (Agarwal and Mehendale, 1983). Furthermore, prior exposure to chlordecone at 10 ppm in the diet for 15 days did not potentiate the hepatotoxicity or lethality of tribromomethane. These findings contrast with those for chloroform in which hepatotoxicity was increased after previous exposure to chlordecone (Hewitt et al., 1979). SGPT activity was increased when tribromomethane and carbon tetrachloride were administered to Long-Evans rats by intraperitoneal injection together at doses that alone did not cause any apparent increase in SGPT activity (0.2 ml/kg [578 mg/kg] and 0.1 ml/kg, respectively) (Harris et al., 1982). These findings are indicative of an interactive hepatotoxicity for these two compounds.

Tribromomethane was administered by gavage in 10% emulphor (in deionized water) to CD-1 mice at doses of 0, 50, 125, or 250 mg/kg per day for 14 days (Munson et al., 1982). Humoral and cellular immunity, assessed by measuring the number of splenic IgM antibody-forming cells and the delayed-type hypersensitivity response, were depressed in the high dose male mice. In addition, liver weight and SGOT levels were increased and serum glucose and BUN levels were decreased in the high dose animals.

Tribromomethane also caused a dose-dependent suppression in hepatic phagocytosis (assessed by measuring the vascular clearance rate of ^{125}I-labeled *Listeria monocytogenes*) in ICR mice given doses of 0.3, 12.5, or 125 mg/kg for 90 days (Munson et al., 1978). Administration of tribromomethane to ICR mice at doses of 100 or 400 mg/kg per day, for 60 days, caused a decrease in response rate in a schedule-controlled performance test (Balster and Borzelleca, 1982). Tribromomethane had minimal or no effect in other behavioral tests (screen test, swimming endurance, passive-avoidance learning, cling test, hole-board test). In studies of neurochemical changes produced by drinking water contaminants, tribromomethane did not affect catecholaminergic systems or serotonin metabolism in the brain of Swiss Webster ICR mice (Dewey et al., 1978; Martin et al., 1978). Tribromomethane inhibited the incorporation of $^{32}P_i$ and [^{3}H]glycerol into phospholipid fractions of liver slices prepared from Wistar rats (Koyama and Nakazawa, 1986). These effects of tribromomethane on triacylglycerol synthesis were attributed to inhibition of glycerophosphate acyltransferase, phosphatidate phosphatase, and diacylglycerol acyltransferase activities.

Reproductive and Developmental Toxicity

Kavlock et al. (1979) performed teratology studies of organic concentrates prepared from the drinking water of five U.S. cities. In addition, because low molecular weight organohalides may be lost during the concentration procedure, a synthetic mixture was prepared based on the EPA monitoring survey of the concentrations of these compounds in 110 U.S. cities. The latter mixture contained 68.9% chloroform, 16.4% bromodichloromethane, 10.0% chlorodibromomethane, and 3.6% tribromomethane. Each of these preparations, dissolved in dimethyl sulfoxide, was administered by gavage to groups of pregnant CD-1 mice on gestation days 7-14 at dose levels equivalent to 300, 1,000, and 3,000 times the anticipated human exposure. The mice that were administered the synthetic mixture at 3,000 times the human exposure level received 10.3 mg organohalide/kg per day (the tribromomethane dose level was 0.37 mg/kg per day). No effects on fetal weight, mortality, or the occurrence of skeletal or visceral anomalies were observed in any of the exposed groups.

Ruddick et al. (1983) administered chloroform to pregnant Sprague Dawley rats by gavage from day 6 to day 15 of gestation at doses of 100, 200, or 400 mg/kg and tribromomethane, bromodichloromethane, and chlorodibromomethane at doses of 50, 100, or 200 mg/kg. Corn oil was used as the vehicle for all studies. Only tribromomethane did not have an effect on maternal body weight gain. No histopathologic changes were observed for any of the four trihalomethanes in

any of the dams or fetuses, nor were there any changes in the number of resorption sites, number of fetuses per dam, average fetal weight, or occurrence of visceral anomalies. Skeletal anomalies, including the appearance of a 14th rib, intraparietal deviations, and delayed ossification of sternebrae, were observed in the tribromomethane, chloroform, and chlorodibromomethane groups. These anomalies were considered to be indicative of fetotoxic effects.

Carcinogenicity

Results of carcinogenesis studies of chloroform in Osborne-Mendel rats and B6C3F$_1$ mice (NCI, 1976a; IARC, 1979) and of 2-year studies of the chemically related chlorodibromomethane and bromodichloromethane in F344/N rats and B6C3F$_1$ mice (NTP, 1985, 1987) are shown in Table 1. For the chloroform studies, rats and mice were administered chloroform in corn oil by gavage 5 days per week for 78 weeks. The doses were 90 and 180 mg/kg for male rats and 125 and 250 mg/kg for female rats for 22 weeks; doses for female rats were then reduced to 90 and 180 mg/kg, resulting in time-weighted-average (TWA) doses of 100 and 200 mg/kg. Doses for male mice were 100 and 200 mg/kg for 18 weeks and then were increased to 150 and 300 mg/kg (TWA doses of 138 and 277 mg/kg); doses for female mice were 200 and 400 mg/kg for 18 weeks and then were increased to 250 and 500 mg/kg (TWA doses of 238 and 477 mg/kg). Administration of chloroform produced dose-related increases in the incidences of kidney epithelial neoplasms in male rats (vehicle control, 0/19; low dose, 4/50; high dose, 12/50) and of hepatocellular carcinomas in male and female mice (male: 1/18; 18/50; 44/45; female: 0/20; 36/45; 39/41).

TABLE 1. PRIMARY SITES OF NEOPLASTIC RESPONSES IN RATS AND MICE ADMINISTERED TRIHALOMETHANES (a)

Chemical	Dose (mg/kg per day)	Liver	Kidney	Large Intestine
Chloroform (b)				
Osborne-Mendel rats				
Male	0, 90, 180	–	+	–
Female	0, 100, 200	–	–	–
B6C3F$_1$ mice				
Male	0, 138, 277	+	–	–
Female	0, 238, 477	+	–	–
Bromodichloromethane (c)				
F344/N rats				
Male	0, 50, 100	–	+	+
Female	0, 50, 100	–	+	+
B6C3F$_1$ mice				
Male	0, 25, 50	–	+	–
Female	0, 75, 150	+	–	–
Chlorodibromomethane (d)				
F344/N rats				
Male	0, 40, 80	–	–	–
Female	0, 40, 80	–	–	–
B6C3F$_1$ mice				
Male	0, 50, 100	±	–	–
Female	0, 50, 100	+	–	–

(a) Response: +, compound-related neoplastic lesions; ±, equivocal evidence of compound-related neoplastic lesions; –, no evidence of compound-related neoplastic lesions
(b) NCI, 1976a; IARC, 1979
(c) NTP, 1987; Dunnick et al., 1987
(d) NTP, 1985; Dunick et al., 1985

Administration of chlorodibromomethane by gavage in corn oil to $B6C3F_1$ mice for 2 years at doses of 50 or 100 mg/kg also produced increases in the incidence of hepatocellular neoplasms in each sex (NTP, 1985; Dunnick et al., 1985). Chlorodibromomethane was not carcinogenic in F344/N rats administered doses of 40 or 80 mg/kg for 2 years.

Oral administration of bromodichloromethane to F344/N rats for 2 years at 50 or 100 mg/kg resulted in increased incidences of tubular cell neoplasms in the kidney and adenocarcinomas and adenomatous polyps in the large intestine of both males and females (NTP, 1987; Dunnick et al., 1987). Administration of bromodichloromethane to $B6C3F_1$ mice for 2 years at doses of 25 or 50 mg/kg (males) and 75 or 150 mg/kg (females) resulted in increased incidences of tubular cell neoplasms in the kidney of male mice and hepatocellular neoplasms in female mice.

The carcinogenicity studies of tribromomethane, the other trihalomethane formed during chlorination of water, are described in this report.

Injection of tribromomethane at 48 mg/kg into strain A mice for 8 weeks (24 intraperitoneal injections), followed by a 16-week observation period, caused a significant increase in the number of pulmonary adenomas per mouse compared with the number in mice injected with 0.9% sodium chloride (Theiss et al., 1977). In initiation/promotion assays reported by Pereira et al. (1982), single doses of either chloroform (1.5 mmol/kg) or tribromomethane (0.8 mmol/kg, 202 mg/kg) did not cause increases in the incidence of γ-glutamyl transpeptidase (GGTase)-positive foci in intact or partially hepatectomized male Sprague Dawley rats promoted with phenobarbital (500 ppm in the drinking water for 47 days). The incidence of GGTase-positive foci in the liver of rats administered an initiating dose of diethylnitrosamine (0.5 mmol/kg body weight) and promoted with chloroform (1.5 mmol/kg two times per week for 53 days) was not different from that in rats given diethylnitrosamine or chloroform alone.

Epidemiologic studies indicate that there may be an association between trihalomethanes in drinking water and increased frequencies of bladder, colon, rectal, or pancreatic cancer in humans (Kraybill, 1980; Cotruvo, 1981; Carlo and Mettlin, 1980; Isacson et al., 1983; Crump, 1983). However, because of a number of potential confounding variables in these studies (e.g., personal habits, limited information on residential histories and past exposures), the data should be considered preliminary and incomplete. Lawrence et al. (1984) found no evidence of a relationship between exposure to trihalomethanes in drinking water and colorectal cancers in white female teachers in upstate New York. Cantor et al. (1987) demonstrated an association between consumption of chlorinated surface water and urinary bladder cancer in 10 areas of the United States.

Genetic Toxicity

Trihalomethanes are usually not mutagenic when tested in Salmonella by the plate incorporation method (Simmon et al., 1977; Rapson et al., 1980), possibly because concentrations are reduced by evaporation during incubation. There are reports of induction of gene reversion by base-pair substitution in *Salmonella typhimurium* strains TA100 and TA1535 when exposure to tribromomethane occurred within the closed environment of a desiccator in the absence of exogenous metabolic activation (Simmon and Tardiff, 1978; Simmon, 1981). When tribromomethane was tested by the NTP in a preincubation procedure in *S. typhimurium*, the evidence for mutagenicity was equivocal in strain TA100 in the absence of S9 and in strains TA97 and TA98 in the presence of Aroclor 1254-induced male Syrian hamster liver S9; tribromomethane produced no significant increases in revertant colonies in strains TA1535 or TA1537 with or without exogenous metabolic activation (Haworth et al., 1983; Table E1). Bromodichloromethane and chlorodibromomethane were also reported to be mutagenic in strain TA100 in the absence of metabolic activation (Simmon and Kauhanen, 1978; Simmon and Tardiff, 1978), whereas chloroform was not mutagenic (Gocke et al., 1981; Van Abbe et al., 1982). NTP test results for bromodichloromethane and chlorodibromomethane in Salmonella were negative (Mortelmans et al., 1986; Zeiger et al., 1987).

Tribromomethane induced trifluorothymidine resistance in mouse L5178Y cells with and without Aroclor 1254-induced male F344 rat liver S9 (Table E2). Tribromomethane also produced a significant increase in sex-linked recessive lethal mutations in Drosophila when administered to adult males by feeding; no induction of mutations was observed when tribromomethane was administered by abdominal injection (Woodruff et al., 1985; Table E5). A test for induction of reciprocal translocations in adult male Drosophila exposed to tribromomethane in feed was negative (Table E6).

Maddock and Kelly (1980) reported that exposure to tribromomethane did not cause an increase in the frequency of sister chromatid exchanges (SCEs) in 72-hour oyster toadfish leukocyte cultures. One of two NTP laboratories that tested tribromomethane for cytogenetic effects in cultured Chinese hamster ovary (CHO) cells reported that it produced an increase in both SCEs and chromosomal aberrations in the absence, but not in the presence, of exogenous metabolic activation; the second laboratory observed no such increases (Galloway et al., 1985; Tables E3 and E4). Results of NTP in vitro cytogenetic studies of bromodichloromethane and chlorodibromomethane were negative for induction of chromosomal aberrations, but treatment with chlorodibromomethane did induce an increase in SCEs in the presence of induced rat liver S9 (unpublished results). Tribromomethane, chlorodibromomethane, bromodichloromethane, and chloroform were all reported to induce SCEs and cell cycle delays in human lymphocytes treated in vitro (Morimoto and Koizumi, 1983).

Morimoto and Koizumi (1983) also reported induction of SCEs in bone marrow cells of ICR/SJ mice given oral doses of 25-200 mg/kg per day of tribromomethane, chlorodibromomethane, bromodichloromethane, or chloroform for 4 days. The cytogenetic effects of a single intraperitoneal injection of chloroform or tribromomethane on bone marrow cells of male B6C3F$_1$ mice have also been examined in in vivo studies sponsored by the NTP (Tables E7 and E8); neither chemical induced chromosomal aberrations in bone marrow cells under the standard protocol (cells harvested 23-24 hours after treatment). Chloroform induced a positive trend for SCEs at doses of 0.42-1.67 mmol/kg (50-200 mg/kg) and 1.67-6.70 mmol/kg (200-800 mg/kg) under the standard protocol. Tribromomethane did not induce SCEs with the standard protocol; however, when cells were sampled 36 hours after exposure, the trend test was positive for induction of SCEs at doses of 0.79-3.17 mmol/kg (200-800 mg/kg), and a significant response was observed at the highest dose tested. In contrast to the results of Morimoto and Koizumi, NTP in vivo cytogenetic tests with chlorodibromomethane showed no induction of SCEs or chromosomal aberrations in mice after an intraperitoneal injection of up to 2.40 mmol/kg (NTP, unpublished results).

Intraperitoneal injection of tribromomethane at doses of 200-800 mg/kg induced a positive trend for micronucleated polychromatic erythrocytes in the bone marrow of B6C3F$_1$ mice (Table E9). Chloroform induced a similar increase in the incidence of micronuclei in bone marrow polychromatic erythrocytes of B6C3F$_1$ mice.

Study Rationale

Tribromomethane was selected for 2-year oral toxicology and carcinogenesis studies as part of an organohalide class evaluation because of its presence in drinking water and potential for human exposure, because carcinogenicity data on this chemical were insufficient, and because chloroform (trichloromethane) is known to cause cancer in animals.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRIBROMOMETHANE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF TRIBROMOMETHANE

Tribromomethane was obtained in three lots from Freeman Industries (Table 2). Purity, identity, and stability analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the tribromomethane studies are on file at NIEHS.

The infrared, ultraviolet, and nuclear magnetic resonance spectra of all lots (representative spectra presented in Figures 1 and 2) were consistent with those in the literature (Aldrich Library; Sadtler Standard Spectra; CRC, 1975). Purity was determined by elemental analysis, Karl Fischer water analysis, potentiometric titration in methanol solution with 0.01 N sodium hydroxide for acidic components, and gas chromatography with flame ionization detection, a nitrogen carrier at a flow rate of 65 or 70 ml/minute, and a 20% SP2100/0.1% Carbowax 1500 column (system 1) or a 10% Carbowax 20M-TPA column (system 2). Results of elemental analyses of all lots were in agreement with the theoretical values.

Lot no. 71221 was obtained as a clear, colorless liquid with a boiling point of 149°-150° C and a density at 24° C of 2.8609 ± 0.0004 g/ml. Cumulative data indicated that this lot was approximately 95% pure. Lot no. 71221 contained 0.014% water and 10.64 ppm free acid. Fifteen impurities with a combined area 3.7% that of the major peak were detected by gas chromatographic system 1. The area of the largest impurity peak was 2.8% that of the major peak. This impurity was identified as chlorodibromomethane by gas chromatography/mass spectroscopy with a 10% SP2100 column and a helium carrier at a flow rate of 30 ml/minute. Further confirmation of the identity of this impurity was obtained by gas chromatographic system 1 with spiked and unspiked samples. Eleven impurities were detected by gas chromatographic system 2. Two impurities had areas of 0.90% and 3.2% relative to that of the major peak. The remaining impurities had a combined relative area of 0.65%.

Lot no. 33595 was obtained as a clear, slightly viscous liquid with a density at 22°-23° C of 2.8621 ± 0.0005 g/ml. Cumulative data indicated that lot no. 33595 was approximately 95% pure. This lot contained 0.028% water and less than 5 ppm free acid. Thirteen impurities that had a combined area 4.4% that of the major peak were detected by gas chromatographic system 1. The three largest peaks had areas 1.4%, 1.4%, and 0.92% that of the major peak. These impurities were not identified. Thirteen impurities were detected by gas chromatographic system 2. Two impurities had areas of 1.3% and 1.6% relative to that of the major peak. These impurities were not identified. The remaining impurities had a combined relative area of 0.64%.

TABLE 2. IDENTITY AND SOURCE OF TRIBROMOMETHANE USED IN THE GAVAGE STUDIES

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
71221	71221	33595	33595; F11017
Date of Initial Use			
12/7/78	4/2/79	3/6/80	Lot no. 33595--2/23/81; lot no. F11017--5/28/82
Supplier			
Freeman Industries (Tuckaho, NY)	Freeman Industries (Tuckaho, NY)	Freeman Industries (Tuckaho, NY)	Freeman Industries (Tuckaho, NY)

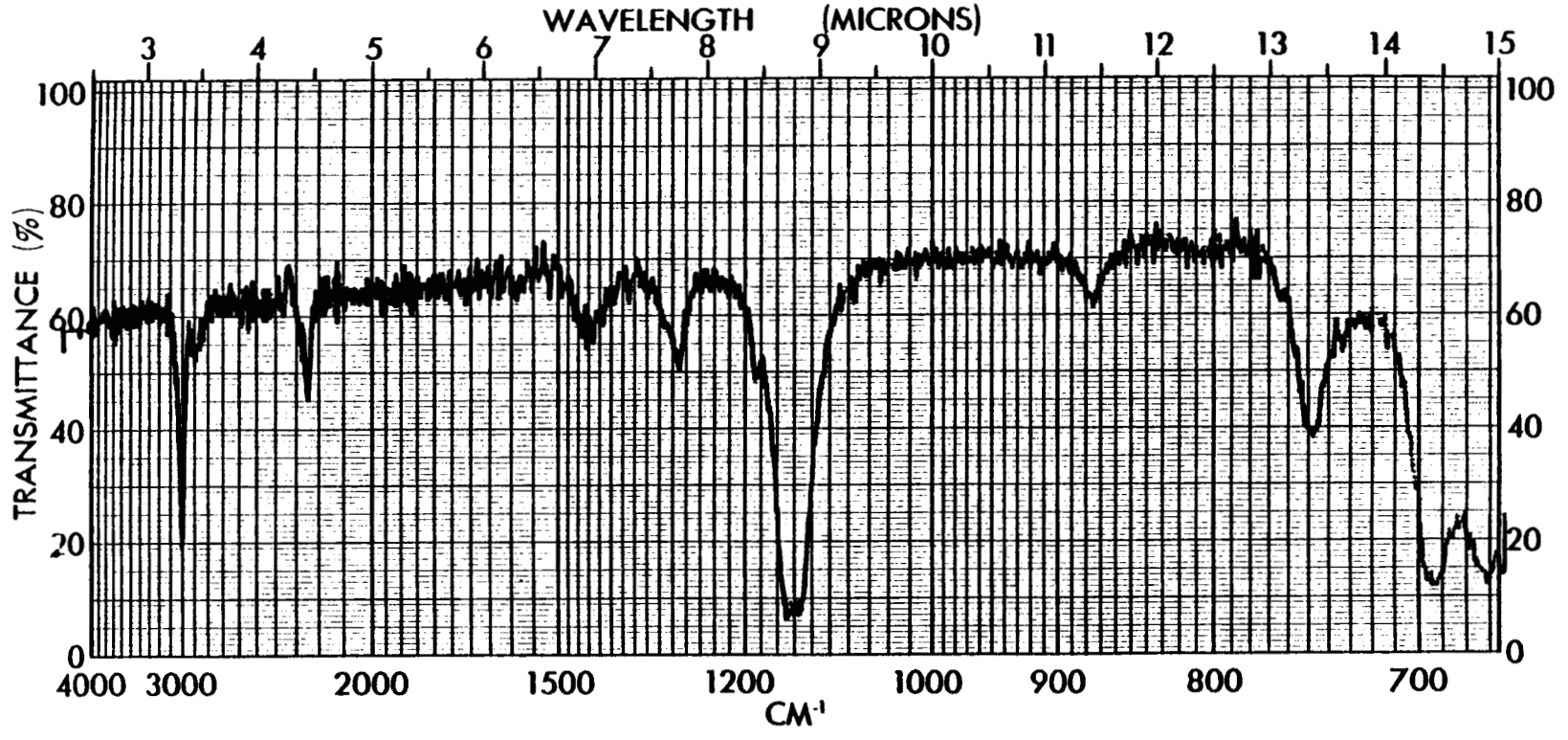


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF TRIBROMOMETHANE (LOT NO. 71221)

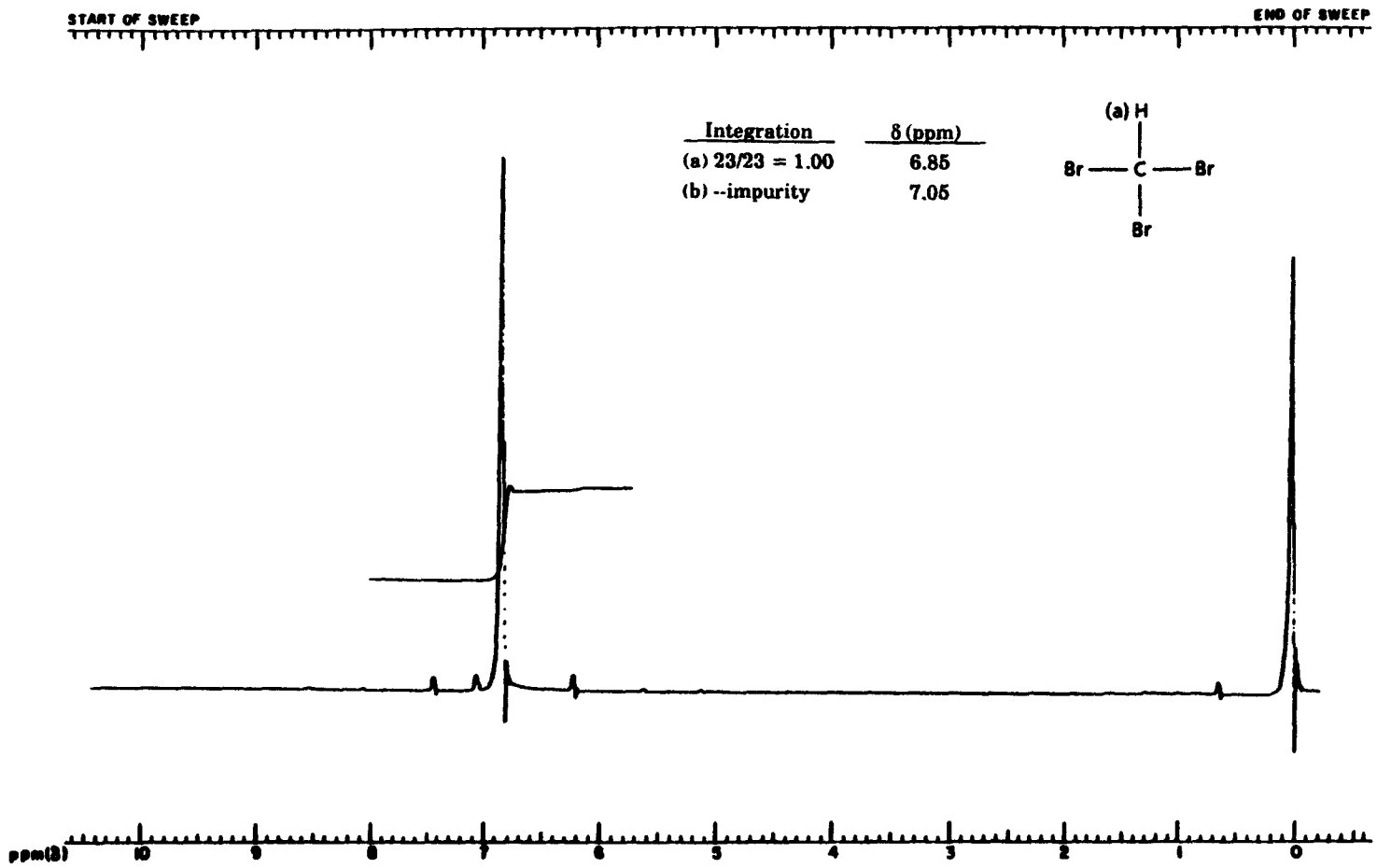


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TRIBROMOMETHANE (LOT NO. 71221)

Cumulative data indicated that lot no. F11017, obtained as a clear, colorless liquid, was at least 97% pure. Lot no. F11017 contained 0.012% water and less than 25 ppm free acid. Twelve impurities that had a combined area 2.6% that of the major peak were detected by gas chromatographic system 1. The largest peaks had areas 1.3% and 0.8% that of the major peak. These impurities were not identified. However, analysis with standards and spiked samples on this gas chromatographic system indicated that chlorodibromomethane was not present at a concentration greater than 0.01%. Gas chromatographic system 2 detected 10 impurities with a total area 2.0% that of the major peak. The largest impurity had an area 1.4% that of the major peak. This impurity was not identified.

Stability studies performed by gas chromatography with the same column as that described above for system 2 indicated that tribromomethane was stable as a bulk chemical when kept for 2 weeks at temperatures of 5° C or lower. Some deterioration was observed at 25° C. The study laboratory stored several portions at −20° C as reference samples, and the rest was stored at 0° ± 5° C. For the 2-year studies, lot no. 33595 was distributed into amber vials that were sealed under nitrogen and stored at −18° C or lower; lot no. F11017 was distributed into serum vials that were flushed with argon and stored under the same conditions. Aliquots of tribromomethane used for dose preparation were stored at 0° ± 16° C for 1 month or less. Confirmation of the stability of the bulk chemical during the toxicology studies was shown by gas chromatographic analysis with the same column as that described above for system 2. No deterioration was seen over the course of the studies. The identity of the study chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Tribromomethane and corn oil were mixed to give the desired concentrations (Table 3). Dose mixture stability studies were performed by gas chromatography of methanol extracts with the same column as that described for system 1. Tribromomethane at 2% (w/v) in corn oil was found to be stable when stored at room temperature for up to 7 days. In the 13-week studies, dose mixtures were stored at 0° ± 5° C for no longer than 14 days. In the 2-year studies, dose mixtures were stored at 0° ± 6° C for no longer than 7 days.

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF TRIBROMOMETHANE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Tribromomethane was weighed into 50-ml serum vials, sufficient corn oil was added to bring the total volume of the mixture to 20 ml, and the vials were vigorously shaken by hand for 10 sec, producing a clear solution	Same as single-administration studies	Weighed tribromomethane was mixed by inversion with the appropriate volume of corn oil in a ground-glass stoppered cylinder until visual homogeneity was attained	Same as 13-wk studies
Maximum Storage Time			
1 d	1 wk	2 wk	1 wk
Storage Conditions			
4° C	4° C under nitrogen	0° ± 5° C in the dark under nitrogen	0° ± 6° C in the dark under nitrogen until 4/15/81 when nitrogen was replaced with argon

Analysis of dose mixtures was conducted periodically at the study laboratory by gas chromatography (same column as that described for system 1) after extraction with methanol containing 0.1 mg/ml *n*-amyl alcohol as an internal standard. The results of analysis of dose mixtures in the 13-week studies are shown in Table 4. During the 2-year studies, the dose mixtures were analyzed periodically. Concentrations ranged from 93% to 561% of the target values; the second highest concentration observed was 118% of the target value (Table 5). The dose mixture containing 561% of the target concentration was administered to low dose male rats once and to low dose female rats twice. Because 40/42 dose mixtures analyzed were within 10% of the target concentrations, the dose mixtures were estimated to have been within specifications 95% of the time throughout the entire study. Results of periodic referee analysis performed by the analytical chemistry laboratory were in generally good agreement with the results from the study laboratory (Table 6).

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRIBROMOMETHANE

Date Mixed	Concentration of Tribromomethane in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
03/06/80	2.4	3.9	(b) 162.5
	5	4.9	98
	10	7.3	(b) 73
	20	18.4	92
	40	38.1	95.3
	80	73.5	91.9
03/28/80	2.4	2.2	(c) 91.7
	10	9.4	(c) 94

(a) Results of duplicate analysis
(b) Out of specifications
(c) Remix

TABLE 5. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

Date Mixed	Concentration of Tribromomethane in Corn Oil for Target Concentration (mg/ml) (a)		
	10	20	40
02/19/81	--	19.8	40.0
03/27/81	10.0	20.0	39.8
04/02/81	--	(b) 112.2	--
04/24/81	10.6	19.5	39.8
07/10/81	10.2	19.6	41.1
09/11/81	9.3	19.3	39.1
10/23/81	10.4	21.2	40.8
11/27/81	10.2	19.3	40.3
02/12/82	10.2	19.2	39.5
04/23/82	10.3	19.5	39.1
06/11/82	(c) 11.8	19.9	39.8
06/14/82	(d) 10.4	--	--
08/20/82	9.9	19.8	40.3
09/10/82	10.9	19.7	40.9
12/03/82	9.3	20.4	39.2
01/07/83	10.2	19.7	40.5
Mean (mg/ml)	10.3	25.9	40.0
Standard deviation	0.64	23.87	0.68
Coefficient of variation (percent)	6.2	92.2	1.7
Range (mg/ml)	9.3-11.8	19.2-112.2	39.1-41.1
Number of samples	13	15	14

(a) Results of duplicate analysis
(b) Used for 2 days; analysis performed because of animals' toxic response. If this value is excluded, the mean and standard deviation would be 19.8 and 0.52 mg/ml.
(c) Out of specifications; used 1 day.
(d) Remix; not included in mean.

TABLE 6. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
04/24/81	20	19.5	19.11
10/23/81	40	40.8	40.0
04/23/82	10	10.3	10.16
09/10/82	20	19.7	19.6

(a) Results of duplicate analysis
(b) Results of triplicate analysis

SINGLE-ADMINISTRATION STUDIES

Five- to six-week-old male and female F344/N rats and 5- to 8-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 2 weeks before the studies began. Groups of five rats and mice of each sex were administered a single dose of 125, 250, 500, 1,000, or 2,000 mg/kg tribromomethane in corn oil by gavage and then were observed for 14 days. No controls were used. Animals were housed five per cage and received water and feed ad libitum. Further details of animal maintenance are presented in Table 7. Rats and mice were observed two times per day. A necropsy was performed on at least one animal from each sex and dose group.

FOURTEEN-DAY STUDIES

Eight-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 17 days (rats) or 15 days (mice) before the studies began. Groups of five rats of each sex and groups of five female mice were administered 0, 100, 200, 400, 600, or 800 mg/kg tribromomethane in corn oil by gavage for 14 consecutive days. Groups of five male mice were administered 0, 50, 100, 200, 400, or 600 mg/kg.

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 7. Rats and mice were observed two times per day. Rats were weighed once per day and mice, on days 0 and 14 and at the end of the studies. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of tribromomethane and to determine the doses to be used in the 2-year studies.

Four- to five-week-old F344/N rats and 5- to 6-week-old B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories. Rats and mice were observed for 22 days before the studies began. Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum.

Groups of 10 rats of each sex were administered 0, 12, 25, 50, 100, or 200 mg/kg tribromomethane in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex received 0, 25, 50, 100, 200, or 400 mg/kg on the same schedule. Further experimental details are summarized in Table 7.

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded one time per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 7.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex and 50 female mice were administered 0, 100, or 200 mg/kg tribromomethane in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 male mice were administered 0, 50, or 100 mg/kg tribromomethane on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age, and mice at 6 weeks of age. The rats were quarantined at the study facility for 19 days, and the mice for 16 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIBROMOMETHANE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
125, 250, 500, 1,000, or 2,000 mg/kg tribromomethane in corn oil by gavage; dose vol--3 ml/kg	Rats and female mice--0, 100, 200, 400, 600, or 800 mg/kg tribromomethane in corn oil by gavage; male mice--0, 50, 100, 200, 400, or 600 mg/kg; dose vol--5 ml/kg	Rats--0, 12, 25, 50, 100, or 200 mg/kg tribromomethane in corn oil by gavage; mice--0, 25, 50, 100, 200, or 400 mg/kg; dose vol--5 ml/kg	Rats and female mice--0, 100, or 200 mg/kg tribromomethane in corn oil by gavage; male mice--0, 50, or 100 mg/kg; dose vol--5 ml/kg
Date of First Dose			
12/7/78	4/2/79	3/6/80	Rats--2/23/81; mice--3/6/81
Date of Last Dose			
N/A	4/15/79	6/4/80	Rats--2/14/83; mice--2/25/83
Duration of Dosing			
Single dose	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 1 × h for 3 h after dosing and 2 × d thereafter	Observed 2 × d; rats weighed 1 × d; mice weighed initially, after 14 d, and at the end of the studies	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed 1 × wk for 12 wk and 1 × mo thereafter
Necropsy and Histologic Examinations			
Necropsy performed on at least one animal of each sex and dose group	Necropsy performed on all animals; histologic exams not performed	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae, stomach, thymus, thyroid gland, trachea, and urinary bladder; liver and spleen of 200 mg/kg male mice and liver of 100 mg/kg male mice were also examined	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups and low dose male rats: abnormal regional lymph nodes, adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nose, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, salivary glands, skin, spleen, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Esophagus, gross lesions, kidneys, liver, lymph nodes, mammary gland, pancreas, pituitary gland, salivary glands, thyroid gland, trachea, and uterus were examined for low dose female rats; bone, gross lesions, liver, lungs, stomach, and trachea were examined for low dose male mice; gross lesions, liver, stomach, thyroid

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIBROMOMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examinations (Continued)			gland, and trachea were examined for low dose female mice
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Portage, MI, and Kingston, NY); mice--Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification			
Ear punch	Ear punch	Ear punch	Ear punch
Time Held Before Study			
14 d	Rats--17 d; mice--15 d	22 d	Rats--19 d; mice--16 d
Age When Placed on Study			
Rats--7-8 wk; mice--7-10 wk	10 wk	Rats--7-8 wk; mice--8-9 wk	Rats--7-8 wk; mice--8 wk
Age When Killed			
Rats--9-10 wk; mice--9-12 wk	12-13 wk	Rats--20-21 wk; mice--21-22 wk	Rats--112 wk; mice--113 wk
Necropsy Dates			
12/21/78	4/17/79-4/21/79	6/19/80-7/1/80	Rats--2/22/83-3/3/83; mice--3/7/83-3/16/83
Method of Animal Distribution			
Assigned to groups such that for a given sex and species all cage weights were approximately equal	Same as single-administration studies	Same as single-administration studies	Animals were assigned to cages according to a table of random numbers
Feed			
Wayne Lab Meal® (Allied Mills, Chicago, IL); available ad libitum	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding			
Aspen Bed (American Excelsior, Baltimore, MD)	Same as single-administration studies	Aspen Bed hardwood chips (American Excelsior, Baltimore, MD) or Beta Chips hardwood chips (Agway, Inc., Syracuse, NY) when Aspen Bed was not available	Same as single-administration studies

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIBROMOMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters			
Nonwoven fiber filters (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--20.6°-23.3° C; hum--17%-49%; fluorescent light 12 h/d; 10 room air changes/h	Temp--17.2°-31.1° C; hum--10%-38%; fluorescent light 12 h/d; 10 room air changes/h	Temp--18°-26° C; hum--44%-78%; fluorescent light 12 h/d; 12 room air changes/h	Temp--17.8°-26.7° C; hum--10%-78%; fluorescent light 12 h/d; 13 room air changes/h

assess their health status. Rats were placed on study at 7-8 weeks of age, and mice at 8 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 7.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 7) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose groups were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the 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 sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the study pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on body weights for this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Other data elements were recorded in the Toxicology Data Management System. The data elements include descriptive information on the chemicals, animals, experimental design, survival, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data: life table tests, logistic regression, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose 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 dosed and vehicle 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 and illustrated by Dinse and Haseman (1986). If the tumor type is nonlethal, this comparison of the time-specific tumor prevalence also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

All 10 rats that received 2,000 mg/kg tribromomethane and 3/5 males and 3/5 females that received 1,000 mg/kg died on the day of dosing (Table 8). Shallow breathing was observed for rats that received 1,000 or 2,000 mg/kg.

FOURTEEN-DAY STUDIES

All rats that received 600 or 800 mg/kg and 1/5 males that received 400 mg/kg tribromomethane died before the end of the studies (Table 9). These rats were lethargic, had labored and shallow breathing, and were ataxic. Increased lacrimation was observed for the 800 mg/kg group. Final mean body weights of rats that received 400 mg/kg were 14% lower than that of vehicle controls for males and 4% lower for females. The thyroid gland was enlarged in 2/5 males and 2/5 females that received 800 mg/kg and in 1/5 males that received 400 mg/kg.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)		
		Initial (b)	Final	Change (c)
MALE (d)				
125	5/5	144 ± 6	202 ± 6	+58 ± 4
250	5/5	142 ± 5	207 ± 7	+65 ± 3
500	5/5	144 ± 8	199 ± 8	+55 ± 3
1,000	2/5	145 ± 3	193 ± 2	+45 ± 3
2,000	0/5	144 ± 4	(e)	(e)
FEMALE (d)				
125	5/5	127 ± 2	148 ± 4	+21 ± 3
250	5/5	126 ± 3	146 ± 4	+20 ± 2
500	5/5	126 ± 2	141 ± 2	+15 ± 1
1,000	2/5	126 ± 2	147 ± 4	+19 ± 1
2,000	0/5	126 ± 1	(e)	(e)

(a) Number surviving/number initially in the group; all deaths occurred on day 1.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) LD_{50} by Spearman-Karber method: 933 mg/kg (95% confidence interval: 669-1,301 mg/kg)
(e) No data are reported due to the 100% mortality in this group.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	143 ± 4	201 ± 5	+58 ± 2	
100	5/5	143 ± 5	210 ± 5	+67 ± 3	104
200	5/5	143 ± 4	202 ± 6	+59 ± 2	104
400	(d) 4/5	144 ± 4	173 ± 6	+27 ± 7	86
600	(e) 0/5	143 ± 3	(f)	(f)	(f)
800	(g) 0/5	143 ± 4	(f)	(f)	(f)
FEMALE					
0	5/5	114 ± 2	138 ± 3	+24 ± 2	
100	5/5	114 ± 2	146 ± 3	+32 ± 2	106
200	5/5	114 ± 2	142 ± 1	+28 ± 2	103
400	5/5	114 ± 2	132 ± 4	+18 ± 4	96
600	(h) 0/5	114 ± 2	(f)	(f)	(f)
800	(i) 0/5	114 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 16
(e) Day of death: 7,8,9,10,10
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 4,4,5,5,6
(h) Day of death: 5,6,6,7,7
(i) Day of death: 5,5,5,6,6

THIRTEEN-WEEK STUDIES

None of the rats died before the end of the studies (Table 10). Final mean body weights of dosed and vehicle control rats were comparable. All males that received 100 or 200 mg/kg tribromomethane and all females that received 200 mg/kg were lethargic. Hepatocellular vacuolization was observed in most male rats (10/10 at 200 mg/kg, 8/10 at 100 mg/kg, 8/10 at 50 mg/kg, 5/10 at 25 mg/kg, 6/10 at 12 mg/kg, and 3/10 vehicle controls). The vacuoles were more numerous in the 200 mg/kg group. This liver lesion, which was not seen in females, was characterized by the presence of well-demarcated vacuoles in the cytoplasm of hepatocytes; larger vacuoles crowded the nuclei towards the periphery of the cells.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	158 ± 3	346 ± 7	+188 ± 5	
12	10/10	160 ± 3	339 ± 4	+179 ± 5	98
25	10/10	158 ± 4	348 ± 5	+190 ± 6	101
50	10/10	160 ± 3	359 ± 6	+199 ± 6	104
100	10/10	158 ± 3	359 ± 4	+201 ± 5	104
200	10/10	159 ± 3	331 ± 4	+172 ± 6	96
FEMALE					
0	10/10	124 ± 1	204 ± 3	+80 ± 2	
12	10/10	124 ± 1	206 ± 4	+82 ± 3	101
25	10/10	124 ± 1	210 ± 2	+86 ± 1	103
50	10/10	123 ± 1	206 ± 4	+83 ± 4	101
100	10/10	124 ± 1	214 ± 3	+90 ± 2	105
200	10/10	124 ± 1	205 ± 4	+81 ± 4	100

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Taken at week 12 of the studies
(d) Mean body weight change of the group ± standard error of the mean

Dose Selection Rationale: Because of the 100% mortality in rats of each sex at 600 mg/kg and lower body weights at 400 mg/kg in the 14-day studies, doses selected for rats in the 2-year studies were 100 and 200 mg/kg tribromomethane, administered in corn oil by gavage, 5 days per week. Hepatocellular vacuolization, which was observed in vehicle control and dosed male rats in the 13-week study, was not considered to be potentially life threatening for the 2-year studies.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 7%-11% lower than those of vehicle controls between weeks 6 and 16 and 12%-28% lower thereafter (Table 11 and Figure 3). Mean body weights of low dose male rats were 5%-14% lower than those of vehicle controls from week 44 to the end of the study. Mean body weights of high dose female rats were 5%-10% lower than those of vehicle controls between weeks 24 and 44 and 10%-25% lower thereafter. Compound-related clinical signs in rats included lethargy in males and females and aggressiveness in males. On April 2, 1981, all low dose rats received 500 mg/kg instead of 100 mg/kg; on April 3, 1981, two-thirds of the low dose female rats again received 500 mg/kg instead of 100 mg/kg. These animals appeared lethargic and sedated after they were dosed.

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

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg No. of Survivors	200 mg/kg Av. Wt. (grams)	200 mg/kg Wt. (percent of veh. controls)	200 mg/kg No. of Survivors
MALE								
1	154	50	145	94	50	146	95	50
2	190	50	184	97	50	184	97	50
3	221	50	220	100	50	221	100	50
4	245	50	246	100	50	246	100	50
5	265	50	268	101	50	262	99	50
6	282	50	275	98	50	261	93	50
7	297	50	287	97	50	275	93	50
8	310	50	302	97	50	283	91	50
9	321	50	317	99	50	295	92	50
10	331	50	328	99	50	302	91	50
11	336	50	332	99	50	307	91	50
12	345	50	345	100	50	322	93	50
16	370	50	367	99	50	331	89	50
20	391	50	386	99	50	343	88	50
24	408	50	396	97	50	354	87	50
28	425	50	412	97	50	363	85	50
32	435	49	421	97	50	364	84	50
36	444	49	426	96	50	367	83	47
40	451	49	431	96	50	369	82	46
44	462	49	436	94	50	368	80	43
48	469	49	445	95	49	378	81	43
52	476	49	449	94	49	378	79	41
56	486	48	455	94	49	391	80	40
60	489	48	452	92	49	383	78	40
64	499	47	454	91	49	390	78	40
68	485	47	449	93	49	381	79	40
72	490	45	452	92	49	387	79	39
76	490	43	446	91	49	379	77	37
80	490	43	443	90	48	373	76	37
84	482	41	444	92	48	377	78	37
88	487	39	449	92	46	387	79	32
92	488	37	443	91	41	369	76	24
96	516	36	442	86	36	373	72	16
100	500	34	442	88	33	377	75	15
104	461	34	424	92	30	364	79	11
FEMALE								
1	116	50	119	103	50	113	97	50
2	135	50	139	103	50	130	96	50
3	149	50	156	105	50	146	98	50
4	160	50	167	104	50	159	99	50
5	171	50	177	104	50	166	97	50
6	180	50	182	101	50	166	92	50
7	185	50	177	96	49	179	97	50
8	190	50	187	98	48	181	95	50
9	193	50	197	102	48	188	97	50
10	199	50	203	102	48	191	96	50
11	201	50	205	102	48	194	97	50
12	207	50	211	102	48	201	97	50
16	215	50	223	104	48	209	97	50
20	223	50	230	103	47	222	100	50
24	228	50	234	103	47	217	95	50
28	236	50	242	103	47	221	94	49
32	241	50	250	104	47	230	95	49
36	248	50	257	104	47	230	93	49
40	252	50	261	104	46	239	95	49
44	264	50	269	102	46	238	90	49
48	273	50	279	102	46	246	90	48
52	282	50	296	105	45	250	89	48
56	290	50	302	104	45	257	89	48
60	298	50	307	103	45	253	85	48
64	308	50	315	102	45	266	86	47
68	315	50	318	101	45	269	85	47
72	322	50	322	100	45	269	84	46
76	328	50	325	99	44	268	82	46
80	336	49	331	99	43	264	79	44
84	338	49	335	99	40	270	80	43
88	347	48	338	97	38	273	79	42
92	348	43	348	100	33	266	76	39
96	353	38	351	99	32	266	75	36
100	359	36	350	97	29	268	75	36
104	350	35	336	96	28	261	75	28

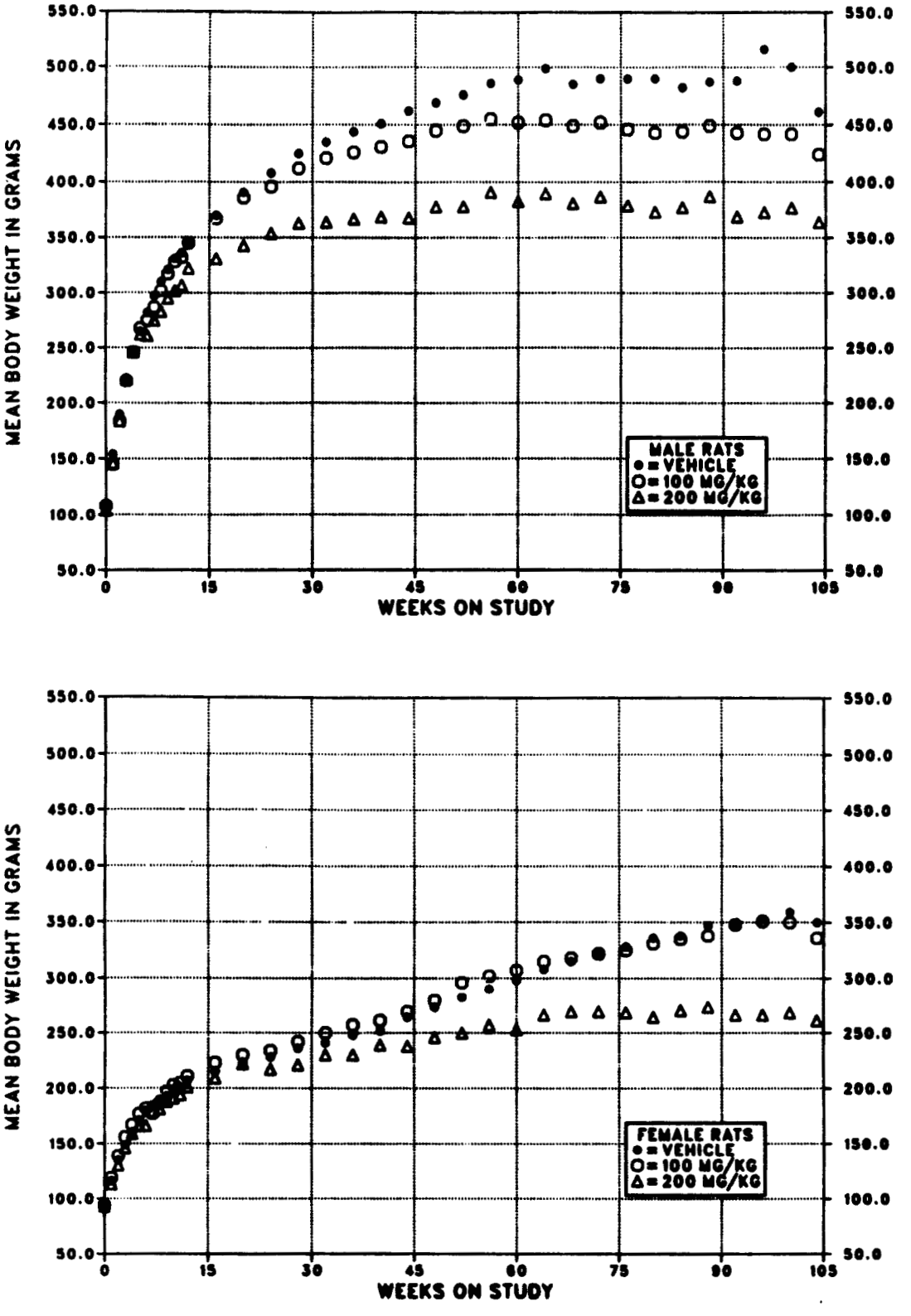


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED TRIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered tribromomethane at the doses used in these studies and for vehicle controls are shown in Table 12 and in the Kaplan and Meier curves in Figure 4. Survival of the high dose group of male rats was significantly lower than that of the vehicle controls after week 91. No significant differences in survival were observed between any groups of female rats.

Pathology and Statistical Analyses of Results

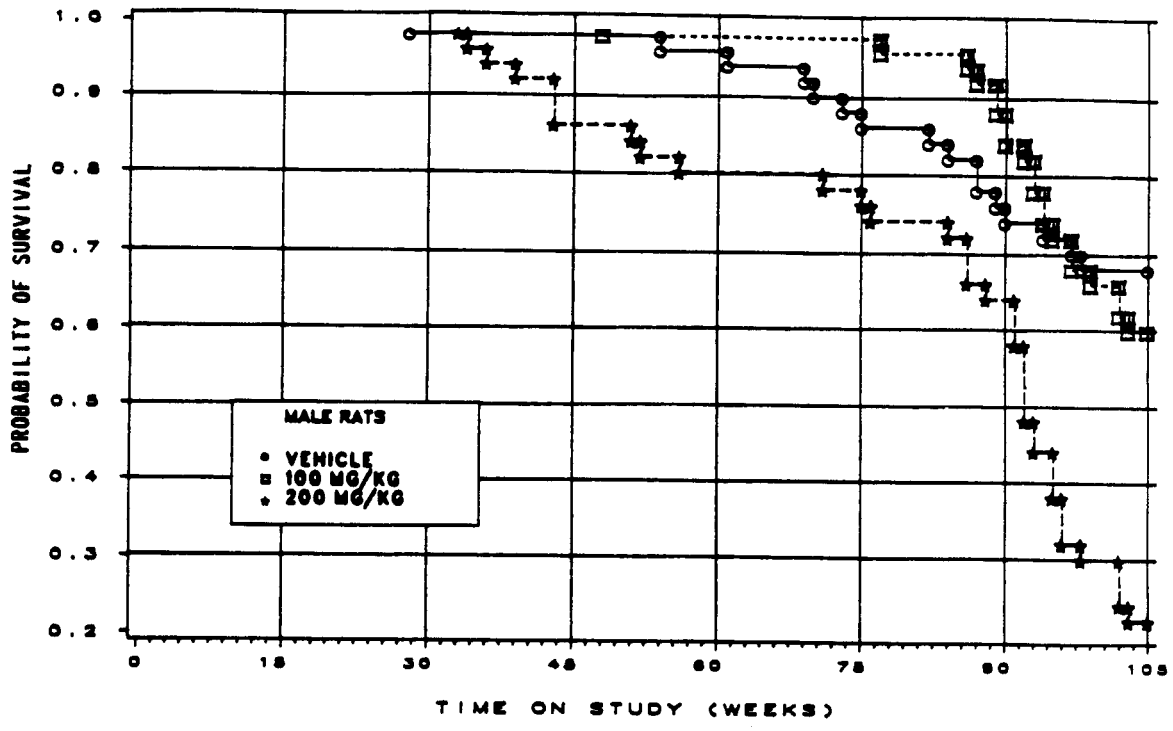
This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the large intestine, liver, salivary glands, prostate gland, forestomach, lung, preputial gland, hematopoietic system, uterus, spleen, anterior pituitary gland, and mammary gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	20	39
Killed at termination	34	30	11
Survival P values (c)	<0.001	0.771	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	(d) 22	21
Accidentally killed	0	0	1
Killed at termination	33	28	28
Died during termination period	1	0	0
Survival P values (c)	0.329	0.150	0.358

(a) First day of terminal-kill period: male--734; female--735
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(d) The deaths of two animals may have been the result of overdosing.



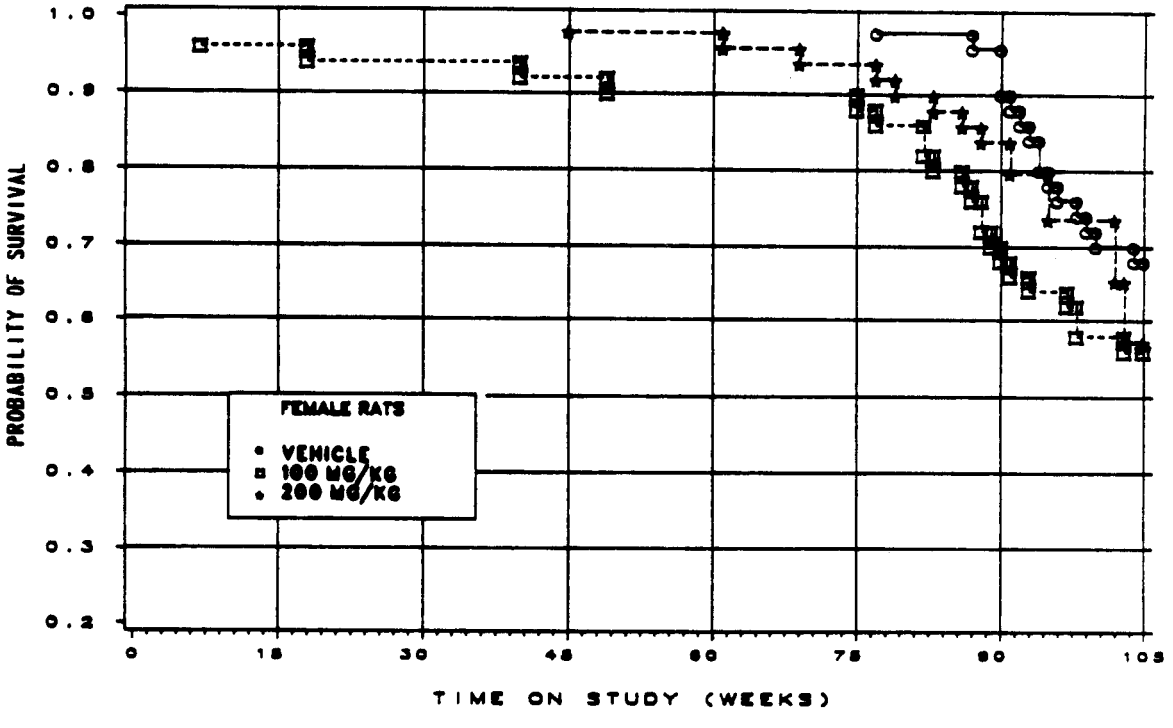


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED TRIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Large Intestine: Adenomatous polyps in female rats and adenomatous polyps or adenocarcinomas (combined) in male and female rats occurred with significant positive trends (Table 13). An adenocarcinoma of the large intestine was diagnosed in one high dose male rat and in two high dose female rats. The adenomatous polyps and adenocarcinomas were pedunculated masses up to 1 cm in diameter and occurred in the colon and rectum. Adenomatous polyps consisted of a thickened, folded, mucosal epithelium overlying a stalk of mature connective tissue. The epithelium was arranged in glandular or tubular patterns and did not show normal differentiation into goblet cells or absorptive cells. The three adenocarcinomas were minimally invasive and arose from adenomatous polyps. These lesions were diagnosed as adenocarcinomas because invasion or extension through the muscularis mucosa occurred and/or the epithelium exhibited marked dysplasia and cellular atypia.

TABLE 13. ANALYSIS OF LARGE INTESTINE TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Adenomatous Polyp			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adenocarcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adenomatous Polyp or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	18.8%
Terminal Rates	0/34 (0%)	0/30 (0%)	1/11 (9%)
Day of First Observation			527
Life Table Tests	P=0.008	(c)	P=0.028
Logistic Regression Tests	P=0.030	(c)	P=0.092
FEMALE			
Adenomatous Polyp			
Overall Rates	0/50 (0%)	(d) 1/50 (2%)	6/50 (12%)
Adjusted Rates	0.0%	3.6%	17.6%
Terminal Rates	0/34 (0%)	1/28 (4%)	3/28 (11%)
Day of First Observation		735	637
Life Table Tests	P=0.004	P=0.461	P=0.013
Logistic Regression Tests	P=0.004	P=0.461	P=0.015
Adenocarcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adenomatous Polyp or Adenocarcinoma (e)			
Overall Rates	0/50 (0%)	(d) 1/50 (2%)	8/50 (16%)
Adjusted Rates	0.0%	3.6%	24.2%
Terminal Rates	0/34 (0%)	1/28 (4%)	5/28 (18%)
Day of First Observation		735	637
Life Table Tests	P<0.001	P=0.461	P=0.003
Logistic Regression Tests	P<0.001	P=0.461	P=0.004

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) Historical incidence of adenomatous polyps, NOS, cystadenomas, NOS, or adenocarcinomas, NOS (combined) at study laboratory (mean): 0/285; historical incidence in NTP studies: 3/1,873 (0.2%)
(c) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.
(d) Gross lesions and target organs in low dose animals were examined according to protocol (see Table 7); 18 large intestines were examined microscopically.
(e) No large intestine tumors have been observed in 1,888 corn oil vehicle control female F344/N rats.

Liver: Chemical-related nonneoplastic lesions, including fatty change, active chronic inflammation, and necrosis, occurred in the liver of dosed rats (Table 14). The fatty change was focal or diffuse in distribution and was characterized by distinct vacuoles within the cytoplasm of hepatocytes. The active chronic inflammation consisted of randomly scattered small foci of macrophages and lymphocytes. The macrophages sometimes contained granular golden pigment and clear vacuoles that probably represented fat. The necrosis that occurred in high dose male rats was minimal in extent and usually consisted of a few scattered individual pyknotic hepatocytes. Necrosis of the liver was decreased in dosed female rats.

The incidence of eosinophilic foci was slightly increased in low dose male rats, and the incidences of mixed cell foci were increased in dosed female rats relative to those in vehicle controls. Decreased incidences of basophilic foci were also observed in dosed female rats. These lesions were characterized by distinct foci of hepatocytes with cytoplasm that stained abnormally. Eosinophilic staining is often associated with increased amounts of smooth endoplasmic reticulum in the cytoplasm, whereas basophilic staining is usually associated with increased amounts of rough endoplasmic reticulum. Mixed cell foci usually contain cells that are either eosinophilic or basophilic and clear cells that contain glycogen or fat.

The incidence of neoplastic nodules in low dose female rats was increased slightly relative to that in vehicle controls. Most of the neoplastic nodules observed in dosed female rats did not fit the current NTP criteria for hepatocellular adenomas (Maronpot et al., 1986); in one high dose female rat, there was sufficient cellular atypia to fit the current criteria for hepatocellular adenoma. The neoplastic nodules were generally large foci with minimal compression caused by

TABLE 14. ANALYSIS OF LIVER LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Fatty Change	23/50 (46%)	49/50 (98%)	50/50 (100%)
Active Chronic Inflammation	0/50 (0%)	29/50 (58%)	23/50 (46%)
Necrosis	7/50 (14%)	3/50 (6%)	20/50 (40%)
Eosinophilic Focus	1/50 (2%)	9/50 (18%)	4/50 (8%)
Basophilic Focus	28/50 (56%)	20/50 (40%)	24/50 (48%)
Mixed Cell Focus	10/50 (20%)	11/50 (22%)	8/50 (16%)
Neoplastic Nodule	4/50 (8%)	2/50 (4%)	0/50 (0%)
Hepatocellular Carcinoma	1/50 (2%)	0/50 (0%)	1/50 (2%)
FEMALE			
Fatty Change	19/50 (38%)	39/49 (80%)	46/50 (92%)
Active Chronic Inflammation	9/50 (18%)	8/49 (16%)	27/50 (54%)
Necrosis	11/50 (22%)	3/49 (6%)	2/50 (4%)
Eosinophilic Focus	0/50 (0%)	2/49 (4%)	2/50 (4%)
Basophilic Focus	28/50 (56%)	15/49 (31%)	13/50 (26%)
Mixed Cell Focus	8/50 (16%)	25/49 (51%)	28/50 (56%)
Neoplastic Nodule (a)			
Overall Rates	0/50 (0%)	4/49 (8%)	2/50 (4%)
Adjusted Rates	0.0%	13.8%	7.1%
Terminal Rates	0/34 (0%)	3/28 (11%)	2/28 (7%)
Day of First Observation		722	735
Life Table Tests	P=0.173	P=0.043	P=0.196
Logistic Regression Tests	P=0.197	P=0.038	P=0.196

(a) Historical incidence at study laboratory (mean ± SD): 6/300 (2% ± 1%); historical incidence in NTP studies: 33/1,945 (2% ± 2%); no hepatocellular carcinomas have been observed.

enlargement of cells or cytoplasmic vacuolization. There was no loss of normal architectural features.

Salivary Glands: Squamous metaplasia of the ducts and chronic active inflammation occurred primarily in the submaxillary salivary gland of dosed rats (squamous metaplasia--male: vehicle control, 0/50; low dose, 15/50; high dose, 31/48; female: 0/49; 10/49; 16/50; chronic active inflammation--male: 0/50; 16/50; 25/48; female: 0/49; 9/49; 18/50). The affected ducts had a thick stratified squamous epithelium instead of the usual single layer of columnar epithelium. Accumulations of neutrophils were sometimes present in the ducts, and there were infiltrations of lymphocytes and macrophages surrounding the ducts and within the interstitium of the gland. The morphologic appearance of these changes was characteristic of a sialodacryoadenitis virus infection.

Prostate Gland: Squamous metaplasia of the prostate gland was observed at increased incidences in dosed male rats (vehicle control, 2/49; low dose, 6/46; high dose, 12/50). Inflammation was observed at similar rates in vehicle control and dosed rats.

Forestomach: Ulcers were observed at increased incidences in dosed male rats (vehicle control, 1/49; low dose, 5/50; high dose, 10/50).

Lung: Chronic active inflammation was observed at increased incidences in dosed male rats (vehicle control, 1/50; low dose, 7/50; high dose, 15/50).

Preputial Gland: Carcinomas and adenomas or carcinomas (combined) in male rats occurred with significant negative trends; the incidence of adenomas or carcinomas (combined) in high dose male rats was significantly lower than that in the vehicle controls (Table 15).

TABLE 15. ANALYSIS OF PREPUTIAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
Adenoma			
Overall Rates	4/41 (10%)	3/38 (8%)	0/34 (0%)
Carcinoma			
Overall Rates	6/41 (15%)	2/38 (5%)	1/34 (3%)
Adjusted Rates	18.4%	7.5%	7.7%
Terminal Rates	5/30 (17%)	1/21 (5%)	0/10 (0%)
Day of First Observation	377	680	716
Life Table Tests	P=0.181N	P=0.235N	P=0.336N
Logistic Regression Tests	P=0.042N	P=0.160N	P=0.083N
Adenoma or Carcinoma (a)			
Overall Rates	10/41 (24%)	5/38 (13%)	1/34 (3%)
Adjusted Rates	31.4%	18.7%	7.7%
Terminal Rates	9/30 (30%)	3/21 (14%)	0/10 (0%)
Day of First Observation	377	632	716
Life Table Tests	P=0.077N	P=0.288N	P=0.134N
Logistic Regression Tests	P=0.008N	P=0.163N	P=0.014N

(a) Historical incidence of preputial gland tumors at study laboratory (mean ± SD): 12/300 (4% ± 2%); historical incidence in NTP studies: 79/1,949 (4% ± 4%)

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a negative trend; the incidence in the high dose group was lower than that in the vehicle controls (Table 16).

Uterus: Stromal polyps in female rats occurred with a significant negative trend; the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 17).

Spleen: Pigmentation occurred at an increased incidence in high dose female rats (vehicle control, 7/49; low dose, 6/28; high dose, 29/50). The golden-brown granular pigment, characteristic of hemosiderin, was present in macrophages.

Anterior Pituitary Gland: Adenomas of the pars distalis in female rats occurred with a significant negative trend; the incidences of adenomas in high dose male and dosed female rats were lower than those in the vehicle controls (Table 18).

Mammary Gland: Fibroadenomas in female rats occurred with a significant negative trend; the incidence in the high dose group was lower than that in the vehicle controls (Table 19). Galactocele was diagnosed in 25/44 vehicle control, 4/42 low dose, and 1/39 high dose female rats.

TABLE 16. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
Overall Rates	14/50 (28%)	9/50 (18%)	5/50 (10%)
Adjusted Rates	34.8%	20.4%	27.8%
Terminal Rates	9/34 (26%)	1/30 (3%)	2/11 (18%)
Day of First Observation	483	600	600
Life Table Tests	P=0.190N	P=0.193N	P=0.364N
Logistic Regression Tests	P=0.019N	P=0.200N	P=0.048N

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 44/300 (15% ± 4%); historical incidence in NTP studies: 321/1,949 (16% ± 9%)

TABLE 17. ANALYSIS OF UTERINE STROMAL POLYPS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
Overall Rates	10/49 (20%)	9/50 (18%)	2/50 (4%)
Adjusted Rates	26.4%	26.1%	6.2%
Terminal Rates	7/34 (21%)	5/28 (18%)	1/28 (4%)
Day of First Observation	630	538	665
Life Table Tests	P=0.040N	P=0.519	P=0.033N
Logistic Regression Tests	P=0.018N	P=0.572N	P=0.019N

(a) Historical incidence of endometrial stromal polyps at study laboratory (mean ± SD): 70/299 (23% ± 3%); historical incidence in NTP studies: 390/1,934 (20% ± 7%)

TABLE 18. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Hyperplasia			
Overall Rates	9/50 (18%)	26/48 (54%)	15/45 (33%)
Adenoma (a)			
Overall Rates	12/50 (24%)	12/48 (25%)	2/45 (4%)
Adjusted Rates	31.8%	31.9%	11.8%
Terminal Rates	9/34 (26%)	6/28 (21%)	1/11 (9%)
Day of First Observation	586	537	616
Life Table Tests	P=0.149N	P=0.508	P=0.130N
Logistic Regression Tests	P=0.024N	P=0.567	P=0.028N
FEMALE			
Hyperplasia			
Overall Rates	9/48 (19%)	15/46 (33%)	7/48 (15%)
Adenoma (b)			
Overall Rates	29/48 (60%)	12/46 (26%)	16/48 (33%)
Adjusted Rates	66.6%	38.1%	46.9%
Terminal Rates	19/33 (58%)	8/26 (31%)	10/27 (37%)
Day of First Observation	610	538	582
Life Table Tests	P=0.043N	P=0.019N	P=0.067N
Logistic Regression Tests	P=0.008N	P=0.003N	P=0.011N

(a) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 107/294 (36% ± 5%); historical incidence in NTP studies: 556/1,898 (29% ± 10%)
(b) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 126/294 (43% ± 11%); historical incidence in NTP studies: 811/1,901 (43% ± 10%)

TABLE 19. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
Fibroadenoma (a)			
Overall Rates	22/50 (44%)	17/50 (34%)	6/50 (12%)
Adjusted Rates	50.9%	51.0%	18.2%
Terminal Rates	14/34 (41%)	12/28 (43%)	4/28 (14%)
Day of First Observation	537	618	543
Life Table Tests	P=0.004N	P=0.509N	P=0.004N
Logistic Regression Tests	P<0.001N	P=0.369N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 104/300 (35% ± 3%); historical incidence in NTP studies: 558/1,950 (29% ± 9%)

SINGLE-ADMINISTRATION STUDIES

All mice that received 2,000 mg/kg, 4/5 males and 2/5 females that received 1,000 mg/kg, and 1/5 males that received 500 mg/kg tribromomethane died before the end of the studies (Table 20). The final mean body weights of mice that survived to the end of the studies were not affected by tribromomethane administration. Males that received 500, 1,000, or 2,000 mg/kg and females that received 1,000 or 2,000 mg/kg were lethargic. Shallow breathing was observed for males that received 1,000 or 2,000 mg/kg.

FOURTEEN-DAY STUDIES

One of five males that received 600 mg/kg and 1/5 females that received 800 mg/kg died before the end of the studies (Table 21). Final mean body weights of dosed and vehicle control mice were comparable. Ataxia and lethargy were observed in males that received 600 mg/kg tribromomethane and in females that received 600 or 800 mg/kg. Raised nodules of the stomach were observed at necropsy in 4/5 males that received 400 mg/kg, in 3/5 males and 2/5 females that received 600 mg/kg, and in 1/5 females that received 800 mg/kg.

TABLE 20. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE (d)				
125	5/5	25.3 ± 0.9	28.2 ± 0.7	+2.9 ± 0.2
250	5/5	25.0 ± 0.5	26.8 ± 0.5	+1.8 ± 0.5
500	(e) 4/5	25.3 ± 0.7	28.5 ± 1.0	+3.2 ± 0.9
1,000	(f) 1/5	25.4 ± 0.7	26.0	+0.7
2,000	(g) 0/5	25.2 ± 1.0	(h)	(h)
FEMALE (i)				
125	5/5	18.5 ± 0.6	19.4 ± 0.7	+0.9 ± 0.2
250	5/5	18.5 ± 0.4	19.4 ± 0.5	+0.9 ± 0.4
500	5/5	18.5 ± 0.5	20.6 ± 0.7	+2.1 ± 0.4
1,000	(j) 3/5	18.8 ± 0.5	21.0 ± 1.0	+2.1 ± 0.9
2,000	(g) 0/5	18.8 ± 0.6	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) LD_{50} by probit analysis: 707 mg/kg (95% confidence interval: 404-1,239 mg/kg)
(e) Day of death: 4
(f) Day of death: 4,4,5,5
(g) Day of death: 1,1,2,2,2
(h) No data are reported due to the 100% mortality in this group.
(i) LD_{50} by Spearman-Karber method: 1,072 mg/kg (95% confidence interval: 768-1,495 mg/kg)
(j) Day of death: 2,8

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 4/5	23.9 ± 0.5	26.0 ± 0.4	+ 2.2 ± 0.5	
50	5/5	23.9 ± 0.6	27.6 ± 0.5	+ 3.7 ± 0.2	106.2
100	5/5	23.8 ± 0.6	26.0 ± 0.8	+ 2.2 ± 0.5	100.0
200	5/5	24.2 ± 0.6	27.6 ± 0.4	+ 3.4 ± 0.5	106.2
400	5/5	23.5 ± 0.7	26.2 ± 0.5	+ 2.7 ± 0.4	100.8
600	(e) 4/5	23.5 ± 0.6	26.5 ± 0.9	+ 2.9 ± 0.4	101.9
FEMALE					
0	5/5	18.5 ± 0.4	20.4 ± 0.4	+ 1.9 ± 0.4	
100	5/5	18.2 ± 0.4	21.4 ± 1.0	+ 3.2 ± 0.7	104.9
200	5/5	18.7 ± 0.4	22.0 ± 0.5	+ 3.3 ± 0.7	107.8
400	5/5	18.4 ± 0.5	21.8 ± 0.4	+ 3.4 ± 0.4	106.9
600	5/5	18.8 ± 0.6	21.2 ± 0.5	+ 2.4 ± 0.3	103.9
800	(f) 4/5	18.9 ± 0.5	20.3 ± 0.3	+ 1.0 ± 0.1	99.5

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death due to error in gavage technique
(e) Day of death: 6
(f) Day of death: 7

THIRTEEN-WEEK STUDIES

One of 10 female mice that received 100 mg/kg tribromomethane died before the end of the studies (Table 22). The final mean body weight of male mice that received 400 mg/kg was 8% lower than that of vehicle controls. Cytoplasmic vacuolization of hepatocytes was observed in the liver of 5/10 males that received 200 mg/kg and 8/10 males that received 400 mg/kg. This dose-related, minimal to moderate change involved only a few cells or was diffuse. Cytoplasmic vacuolization was not observed in hepatocytes of dosed female mice.

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	26.4 ± 0.3	35.2 ± 0.8	+8.8 ± 0.7	
25	10/10	26.8 ± 0.4	36.0 ± 0.9	+9.2 ± 0.7	102.3
50	10/10	27.7 ± 0.4	36.2 ± 0.6	+8.5 ± 0.3	102.8
100	10/10	26.3 ± 0.5	37.7 ± 0.5	+11.4 ± 0.7	107.1
200	10/10	27.1 ± 0.4	34.4 ± 0.7	+7.3 ± 0.4	97.7
400	10/10	26.2 ± 0.5	32.2 ± 0.8	+6.0 ± 0.7	91.5
FEMALE					
0	10/10	20.4 ± 0.3	26.5 ± 0.3	+6.1 ± 0.2	
25	10/10	20.7 ± 0.2	26.9 ± 0.3	+6.2 ± 0.4	101.5
50	10/10	20.4 ± 0.3	26.8 ± 0.5	+6.4 ± 0.4	101.1
100	(e) 9/10	20.6 ± 0.2	27.9 ± 0.9	+7.4 ± 0.8	105.3
200	10/10	20.9 ± 0.3	28.0 ± 0.5	+7.1 ± 0.3	105.7
400	10/10	20.6 ± 0.3	27.5 ± 0.5	+6.9 ± 0.4	103.8

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Taken at week 12 of the studies
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 6

Dose Selection Rationale: Because of deaths of 1/5 males at 600 mg/kg and of 1/5 females at 800 mg/kg in the 14-day studies and dose-related cytoplasmic vacuolization of the liver in males in the 13-week studies, doses selected for mice in the 2-year studies were 50 and 100 mg/kg tribromomethane for males and 100 and 200 mg/kg for females, administered in corn oil by gavage, 5 days per week.

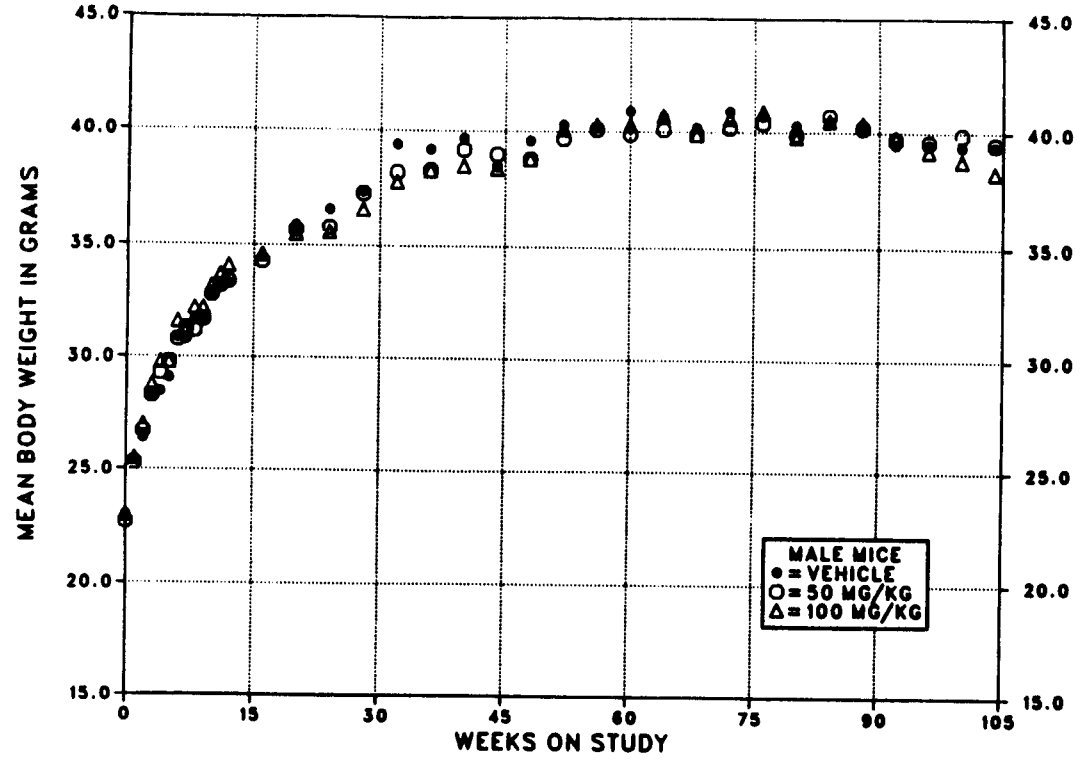
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were comparable throughout the study (Table 23 and Figure 5). Mean body weights of high dose female mice were 5%-16% lower than those of vehicle controls, and mean body weights of low dose female mice were 6%-11% lower from week 28 to the end of the study. No compound-related clinical signs were observed.

TABLE 23. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh. controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh. controls)	High Dose No. of Survivors
MALE				**50 mg/kg**			**100 mg/kg**	
0	23.0	50	22.7	99	50	23.0	100	50
1	25.4	50	25.3	100	50	25.5	100	50
2	26.4	50	26.7	101	50	27.0	102	50
3	28.2	50	28.3	100	50	28.8	102	50
4	28.5	50	29.3	103	50	29.8	105	50
5	29.1	50	29.8	102	50	29.8	102	50
6	30.9	50	30.8	100	50	31.6	102	50
7	30.8	50	31.3	102	50	31.2	101	50
8	31.7	50	31.2	98	50	32.2	102	50
9	31.7	50	31.7	100	50	32.2	102	50
10	32.8	50	32.8	100	50	33.2	101	50
11	33.1	50	33.2	100	50	33.7	102	50
12	33.3	50	33.4	100	50	34.1	102	50
16	34.5	50	34.3	99	50	34.6	100	50
20	35.9	50	35.7	99	50	35.5	99	50
24	36.6	50	35.8	98	49	35.6	97	50
28	37.4	50	37.3	100	49	36.6	98	50
32	39.4	50	38.2	97	49	37.8	96	50
36	39.2	50	38.3	98	49	38.3	98	50
40	39.7	50	39.2	99	49	38.5	97	50
44	38.5	50	39.0	101	49	38.4	100	50
48	39.6	50	38.8	98	49	38.8	98	50
52	40.3	50	39.7	99	49	40.1	100	50
56	40.2	50	40.1	100	48	40.3	100	50
60	40.9	50	39.9	98	48	40.3	99	50
64	40.7	50	40.1	99	48	40.7	100	49
68	40.2	49	39.9	99	48	39.9	99	49
72	40.9	49	40.2	98	48	40.6	99	48
76	40.7	49	40.4	99	46	40.9	100	45
80	40.3	48	39.9	99	46	39.8	99	45
84	40.5	47	40.7	100	46	40.5	100	43
88	40.2	47	40.2	100	45	40.4	100	43
92	39.5	45	39.7	101	44	39.8	101	40
96	39.5	45	39.6	100	41	39.2	99	37
100	39.4	43	39.9	101	37	38.8	98	36
104	39.4	41	39.5	100	37	38.3	97	36
FEMALE				**100 mg/kg**			**200 mg/kg**	
0	18.3	50	18.1	99	50	17.9	98	50
1	19.9	50	19.7	99	50	19.9	100	50
2	21.3	50	21.0	99	50	21.5	101	50
3	22.1	50	21.3	96	50	21.4	97	50
4	22.6	50	22.6	100	50	22.5	100	50
5	22.9	50	22.7	99	50	22.8	100	50
6	25.6	50	23.4	91	50	23.6	92	50
7	24.2	50	23.4	97	50	23.5	97	50
8	24.9	50	24.5	98	50	25.2	101	50
9	25.3	50	24.8	98	50	25.6	101	50
10	26.1	50	24.8	95	50	25.0	96	50
11	26.1	50	25.3	97	50	25.7	98	50
12	26.1	50	26.1	100	50	26.5	102	50
16	27.4	49	26.7	97	50	26.4	96	50
20	28.5	49	27.8	98	50	27.6	97	50
24	28.8	49	27.7	96	50	27.7	96	50
28	31.2	49	28.8	92	50	28.8	92	50
32	32.0	49	29.9	93	50	29.7	93	50
36	32.2	49	30.3	94	50	30.5	95	50
40	33.0	49	31.1	94	50	31.1	94	50
44	33.0	49	31.0	94	50	30.9	94	49
48	34.2	49	31.6	92	50	30.7	90	49
52	35.5	49	33.0	93	50	32.0	90	48
56	36.2	49	33.5	93	50	32.4	90	47
60	37.1	49	33.7	91	50	33.1	89	47
64	37.4	49	34.2	91	50	32.8	88	45
68	37.0	49	33.3	90	50	31.8	86	44
72	38.0	48	34.6	91	46	33.8	89	44
76	37.4	48	34.4	92	44	33.6	90	44
80	36.5	48	33.4	92	37	32.7	90	39
84	36.6	45	33.5	92	32	32.7	89	33
88	38.1	40	33.9	89	27	33.6	88	30
92	37.9	36	34.0	90	25	33.7	89	26
96	38.0	35	34.3	90	21	34.0	89	22
100	38.4	29	34.3	89	17	32.8	85	21
104	38.6	24	34.7	90	15	32.6	84	20



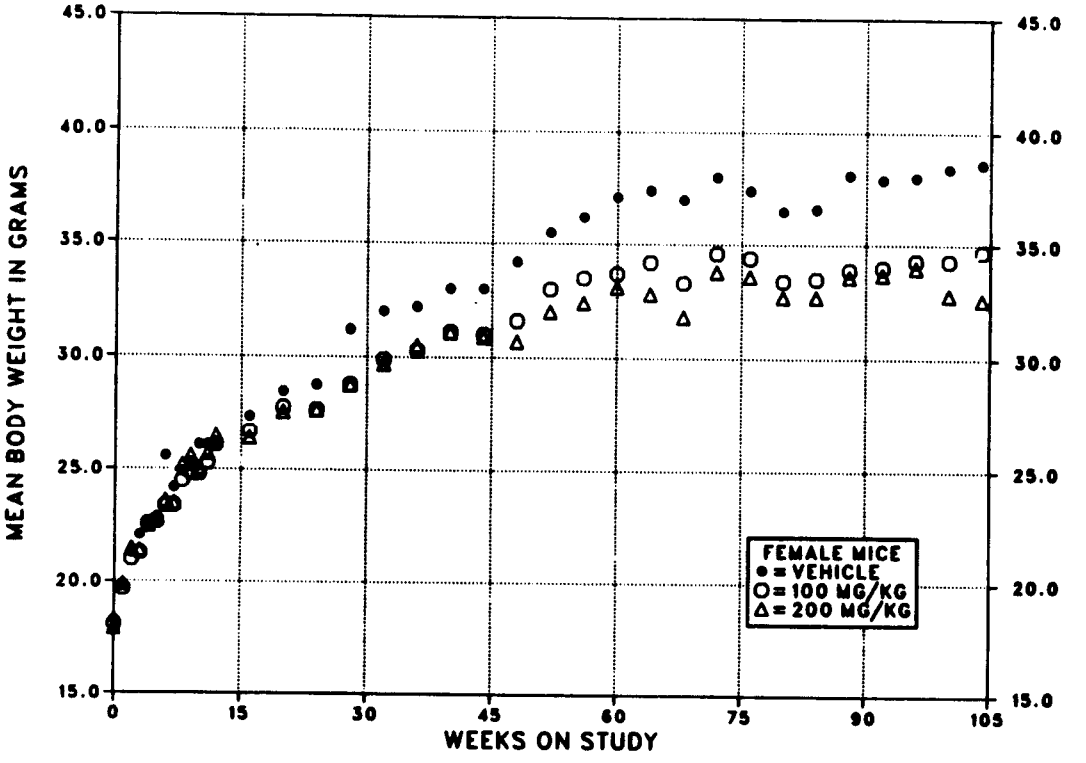


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED TRIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered tribromomethane at the doses used in these studies and for vehicle controls are shown in Table 24 and in the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between any groups of male mice. The survival of the low dose group of female mice was significantly lower than that of the vehicle controls after week 77; the survival of the high dose group was significantly lower than that of the vehicle controls between week 77 and week 100. Survival in each female mouse group was at least 50% at week 92. Reduced survival in the female mouse groups was partly due to a uterovarian infection.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the glandular stomach, thyroid gland, liver, ovary, and lung.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 24. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
MALE (a)				
Animals initially in study	50	50	50	
Nonaccidental deaths before termination (b)	9	13	14	
Killed at termination	41	37	36	
Survival P values (c)	0.231	0.416	0.277	
FEMALE (a)				
Animals initially in study	50		50	50
Nonaccidental deaths before termination (b)	24		35	30
Animals removed, pregnant	1		0	0
Killed at termination	25		13	20
Died during termination period	0		2	0
Survival P values (c)	0.081		0.006	0.097

(a) First day of terminal-kill period: male--730; female--735
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

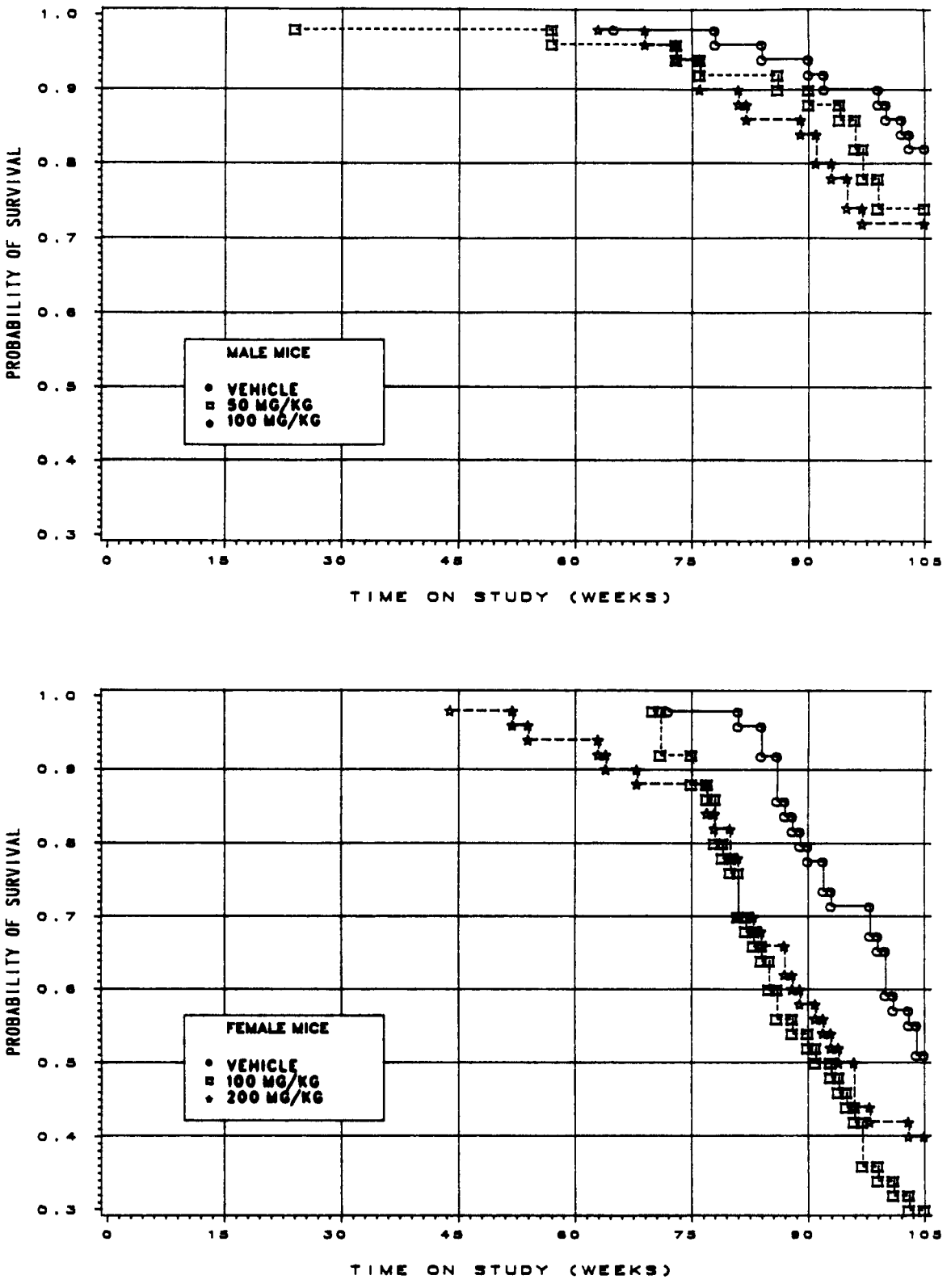


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED TRIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Glandular Stomach: Hyperplasia occurred at slightly increased incidences in dosed mice (male: vehicle control, 1/50; low dose, 5/50; high dose, 6/49; female: 1/47; 4/48; 4/50). This change was characterized by minimal to mild increased depth of the gastric pits and gastric glands. Epithelial cells lining the glands were fully differentiated, and there was no cellular atypia.

Thyroid Gland: Focal or multifocal follicular cell hyperplasia was observed at an increased incidence in high dose female mice (vehicle control, 5/49; low dose, 4/49; high dose, 19/47). Affected areas usually consisted of one to three follicles with enlarged columnar epithelial cells that formed irregular protrusions into the lumens of the follicles. A follicular cell adenoma was seen in 1/46 high dose male mice and 1/49 vehicle control female mice.

Liver: Minimal to mild fatty change consisting of randomly scattered foci of hepatocytes with vacuolated cytoplasm occurred at increased incidences in dosed female mice (vehicle control, 1/49; low dose, 9/50; high dose, 24/50).

Ovary: Abscesses, characteristic of bacterial infection, were observed in 23/45 vehicle control, 31/36 low dose, and 26/49 high dose female mice. Klebsiella sp. were isolated from most of the ovarian and uterine lesions.

Lung: Alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) in male mice occurred with negative trends; the incidences in the high dose group were lower than those in the vehicle controls (Table 25).

TABLE 25. ANALYSIS OF ALVEOLAR/BRONCHIOLAR LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (a)

	Vehicle Control	50 mg/kg	100 mg/kg
Alveolar Epithelial Hyperplasia			
Overall Rates	3/50 (6%)	2/50 (4%)	1/49 (2%)
Adenoma			
Overall Rates	10/50 (20%)	5/50 (10%)	2/49 (4%)
Adjusted Rates	24.4%	12.7%	5.6%
Terminal Rates	10/41 (24%)	4/37 (11%)	2/36 (6%)
Day of First Observation	730	602	730
Life Table Tests	P=0.016N	P=0.178N	P=0.026N
Logistic Regression Tests	P=0.016N	P=0.161N	P=0.026N
Carcinoma			
Overall Rates	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adenoma or Carcinoma (b)			
Overall Rates	11/50 (22%)	7/50 (14%)	2/49 (4%)
Adjusted Rates	26.8%	17.2%	5.6%
Terminal Rates	11/41 (27%)	5/37 (14%)	2/36 (6%)
Day of First Observation	730	507	730
Life Table Tests	P=0.012N	P=0.288N	P=0.015N
Logistic Regression Tests	P=0.009N	P=0.236N	P=0.015N

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes).
(b) Historical incidence at study laboratory (mean ± SD): 66/349 (19% ± 7%); historical incidence in NTP studies: 325/1,985 (16% ± 6%)

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Toxicology and carcinogenesis studies of tribromomethane, a drinking water contaminant resulting from water chlorination, were conducted by gavage administration of this chemical (95%-97% pure) in corn oil to male and female F344/N rats and B6C3F$_1$ mice. Doses selected for the 2-year studies, 100 or 200 mg/kg for male and female rats and female mice and 50 or 100 mg/kg for male mice, were based on results of 14-day and 13-week studies.

In the 14-day studies of tribromomethane, compound-related deaths occurred at doses of 400 mg/kg and higher in male rats and at 600 mg/kg and higher in female rats. In mice, one male that received 600 mg/kg and one female that received 800 mg/kg died. Ataxia, lethargy, and labored breathing were the major clinical signs of tribromomethane intoxication. In the 13-week studies, no deaths were clearly attributable to tribromomethane, nor were significant differences in group mean body weights observed between male or female rats administered 12-200 mg/kg tribromomethane and the vehicle controls. No clear effects of compound administration on survival or body weight were observed for male or female mice administered 25-400 mg/kg tribromomethane. The only compound-related histopathologic change observed was cytoplasmic vacuolization of hepatocytes in male rats and male mice. This lesion, not considered to be life threatening, was observed in rats and mice administered other trihalomethanes, including chloroform (Bull et al., 1986), chlorodibromomethane (Condie et al., 1983; NTP, 1985; Dunnick et al., 1985), and bromodichloromethane (NTP, 1987; Dunnick et al., 1987).

In the 2-year studies, the only group in which tribromomethane caused a reduction in survival, relative to vehicle controls, was the high dose (200 mg/kg) male rats. Survival for all groups of female mice (vehicle control as well as low and high dose groups) was lower than that generally observed for corn oil gavage vehicle control female B6C3F$_1$ mice in 2-year studies (Haseman et al., 1985). Many of the female mice that died early were diagnosed as having utero-ovarian abscesses characteristic of a bacterial infection; Klebsiella sp. were isolated from most of these lesions (Rao et al., 1987a). Thus, a chemical effect on the reduced survival of female mice is not apparent. In spite of the life-shortening Klebsiella infection, survival of each group of female mice was at least 50% at week 92 of the study. Effects of administration of tribromomethane on body weight were apparent for low and high dose male rats, high dose female rats, and low and high dose female mice.

Adenomatous polyps and adenocarcinomas of the large intestine in male and female rats were the only neoplasms with increased incidences in rats or mice administered tribromomethane for 2 years. Neoplasms of the large intestine were also induced in F344/N rats administered bromodichloromethane for 2 years (NTP, 1987; Dunnick et al., 1987). Three neoplasms of the large intestine were observed in male rats dosed with tribromomethane at 200 mg/kg. These lesions were considered to be chemically induced, as a substantial increase in the incidence of the same neoplastic lesions was observed in nine female rats (vehicle control, 0/50; low dose, 1/50; high dose, 8/50) and because neoplasms of the large intestine are uncommon in F344/N rats; the historical incidence is less than 0.2% (3/1,873) in corn oil vehicle control male rats (Table A4a) and is 0% (0/1,888) in corn oil vehicle control female rats (Table B4a). Furthermore, since survival of male rats given 200 mg/kg tribromomethane was markedly reduced, the sensitivity of this group to detect a carcinogenic response was lowered. The morphologic appearance of the neoplasms of the large intestine was the same as that of neoplasms caused by bromodichloromethane in male and female F344/N rats (NTP, 1987; Dunnick et al., 1987) and similar to that of neoplasms of the colon found in humans (Lane et al., 1978). In a feed study with microencapsulated tribromomethane, there was no evidence of carcinogenicity for male or female Wistar rats exposed for 24 months at concentrations of 400, 1,600, or 6,500 ppm (personal communication from Y. Kurokawa, National Institute of Hygienic Sciences, Tokyo, Japan, 1987, to R. Melnick, NTP).

In the current study, neoplastic nodules of the liver were observed in four low dose and two high dose female rats (see Table 14); however, most of these lesions did not fit the current NTP criteria for hepatocellular adenomas (Maronpot

et al., 1986). The incidence of neoplastic nodules was not significantly increased in high dose female rats or in dosed male rats. Thus, the marginal increase in the incidence of neoplastic nodules in female rats was not considered to be chemically induced. A variety of nonneoplastic changes of the liver in rats, including fatty change, active chronic inflammation, and scattered minimal necrosis (males) or mixed cell foci (females), is attributed to chemical administration. Liver toxicity caused by tribromomethane may be due to covalent binding of cellular macromolecules by dibromocarbonyl, a reactive intermediate in the biotransformation of tribromomethane. The changes in the incidences of eosinophilic foci and basophilic foci in the liver of dosed female rats are also indicative of a chemical-induced cellular disturbance.

The inflammatory changes in the lung of dosed male rats and squamous metaplasia of the ducts and inflammatory changes in the salivary glands in dosed male and female rats were similar to those described for a sialodacryoadenitis (SDA) virus infection (Jacoby et al., 1975; Wojcinski and Percy, 1986). Consistent with the suggestion of a viral etiology for these lesions was the detection of antibodies to rat coronavirus/SDA early in the studies. The absence or near absence of these lesions in the vehicle control rats indicates that these lesions may resolve more slowly in dosed rats than in vehicle controls or that the dosed rats may have been more susceptible to reinfection by the virus. In either case, the lesions probably represent a combination of chemical and viral effects.

The increased incidences of squamous metaplasia of the prostate gland in dosed male rats may represent a chemical effect associated with inflammatory lesions in this gland, whereas ulcers of the forestomach in dosed male rats appear to be due to administration of tribromomethane.

Decreased incidences of preputial gland neoplasms and mononuclear cell leukemia in male rats, uterine stromal polyps and mammary gland fibroadenomas in female rats, and pituitary gland adenomas in male and female rats were observed in these studies. It is likely, however, that these changes do not represent direct chemical effects, either because the incidences of these lesions in the dosed groups were not different from historical incidences (for preputial gland, see Table A4b) or because the reduced incidences of these tumors were observed in rats with body weights that were about 10%-25% lower than those of vehicle controls. Rao et al. (1987b) showed that lower body weights are associated with a reduction in the incidences of leukemia in male F344/N rats and of mammary gland fibroadenomas and pituitary gland neoplasms in female F344/N rats. The mechanism by which reduced body weight (or reduced caloric intake) causes these changes is not fully known. Some of the negative trends for neoplasia noted above were also observed in rats administered chlorodibromomethane (mononuclear cell leukemia in males and mammary gland fibroadenomas and uterine stromal polyps in females) or bromodichloromethane (pituitary gland adenomas and mammary gland fibroadenomas in females) and may represent a biologic effect of trihalomethanes.

Toxicologic effects due to administration of tribromomethane to B6C3F$_1$ mice included hyperplasia of the glandular stomach in dosed males and follicular cell hyperplasia of the thyroid gland and cytoplasmic vacuolization of hepatocytes in dosed females. The incidences of cytoplasmic vacuolization of hepatocytes were not increased in dosed male mice, although the lesion had been observed in males at higher doses in the 13-week study.

Results of the carcinogenicity studies of five different trihalomethanes and the doses used in those studies are shown in Tables 26 and 27; expression of the dose as millimoles per kilogram body weight is preferable when making comparisons between related compounds with different molecular weights. Tribromomethane produced a weaker response than bromodichloromethane for large intestine neoplasms in male rats. At nearly equivalent daily doses (0.8 mmol/kg for tribromomethane and 0.6 mmol/kg for bromodichloromethane), the incidence of large intestine

TABLE 26. INCIDENCES OF COMPOUND-RELATED NEOPLASTIC LESIONS IN RATS AND MICE ADMINISTERED TRIHALOMETHANES

Compound	Rats				Mice			
	Kidney Tubular Cell Neoplasms		Large Intestine Neoplasms		Hepatocellular Neoplasms		Kidney Tubular Cell Neoplasms	
	Male	Female	Male	Female	Male	Female	Male	Female
Chloroform (a)								
Vehicle control	0/19	0/20	(b)	(b)	1/18	0/20	(b)	(b)
Low dose	4/50	0/49			18/50	36/45		
High dose	12/50	2/48			44/45	39/41		
Bromodichloromethane (c)								
Vehicle control	0/50	0/50	0/50	0/46	(b)	3/50	1/49	(b)
Low dose	1/50	1/50	13/50	0/50		18/48	2/50	
High dose	13/50	15/50	45/50	12/47		29/50	9/50	
Chlorodibromomethane (d)								
Vehicle control	(b)	(b)	(b)	(b)	23/50	6/50	(b)	(b)
Low dose					14/50	10/49		
High dose					27/50	19/50		
Tribromomethane (e)								
Vehicle control	(b)	(b)	0/50	0/50	(b)	(b)	(b)	(b)
Low dose			0/50	1/50				
High dose			3/50	8/50				
Triiodomethane (f)	(b)	(b)	(b)	(b)	(b)	(b)	(b)	(b)

(a) NCI, 1976a; IARC, 1979
(b) No chemical-related neoplastic effects
(c) NTP, 1987; Dunnick et al., 1987
(d) NTP, 1985; Dunnick et al., 1985
(e) This report
(f) NCI, 1978

TABLE 27. DOSES OF TRIHALOMETHANES ADMINISTERED TO RATS AND MICE IN NCI/NTP CARCINOGENICITY STUDIES (a)

	Male Rats		Female Rats		Male Mice		Female Mice	
	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose
	(mg/kg per day)							
Chloroform (b)	90	180	100	200	138	277	238	477
Bromodichloromethane	50	100	50	100	25	50	75	150
Chlorodibromomethane	40	80	40	80	50	100	50	100
Tribromomethane	100	200	100	200	50	100	100	200
Triiodomethane (b)	71	142	27	55	47	93	47	93
	(mmol/kg per day)							
Chloroform	0.75	1.51	0.84	1.68	1.16	2.32	1.99	3.99
Bromodichloromethane	0.31	0.61	0.31	0.61	0.15	0.31	0.46	0.92
Chlorodibromomethane	0.19	0.38	0.19	0.38	0.24	0.48	0.24	0.48
Tribromomethane	0.40	0.79	0.40	0.79	0.20	0.40	0.40	0.79
Triiodomethane	0.18	0.36	0.07	0.14	0.12	0.24	0.12	0.24

(a) Chloroform and triiodomethane were studied in Osborne-Mendel rats and B6C3F$_1$ mice. Bromodichloromethane, chlorodibromomethane, and tribromomethane were studied in F344/N rats and B6C3F$_1$ mice.
(b) Doses of chloroform and triiodomethane were changed during these studies. Values given are time-weighted averages.

neoplasms was 15 times greater for bromodichloromethane. This difference, however, may in part be due to the reduced survival of the high dose male rats given tribromomethane. Bromodichloromethane also produced a 26% incidence of large intestine neoplasms at the lower dose (0.3 mmol/kg), whereas no large intestine neoplasms were observed in male rats administered 0.4 mmol/kg tribromomethane. In female rats, these two trihalomethanes were similar in potency for induction of large intestine neoplasms. The lack of large intestine tumors in rats administered chlorodibromomethane may be due to the lower daily doses used in that study; the high dose in the chlorodibromomethane study was nearly equal to the low dose in the tribromomethane study.

The finding that tribromomethane was not carcinogenic for the kidney of rats or for the liver of mice was unexpected in light of the high incidences of renal neoplasms in rats and hepatocellular neoplasms in mice exposed to chloroform or bromodichloromethane by the same route of administration. Since the trihalomethanes are metabolized by similar pathways, the key factors that influenced the outcome of the carcinogenicity studies of these compounds were probably differences in doses used, disposition of the parent compound, and/or biochemical characteristics of reactive intermediates.

The first step in the metabolism of trihalomethanes involves an oxygen insertion at the C-H bond, catalyzed by a cytochrome P450-dependent mixed-function oxidase system (Stevens and Anders, 1979). In the next step, nonenzymatic loss of a hydrogen halide results in the formation of a dihalocarbonyl: dichlorocarbonyl from chloroform, dibromocarbonyl from tribromomethane, and diiodocarbonyl from triiodomethane. Because of large differences in bond energies between C-Br and C-Cl (56.2 vs. 70.4 kcal/mol), the dihalocarbonyl formed from bromodichloromethane would be almost exclusively dichlorocarbonyl, and that formed from chlorodibromomethane would be primarily chlorobromocarbonyl. Similarly, because halogens of higher molecular weight are better leaving groups, the reactivity of dihalocarbonyls with cellular nucleophiles should follow the order diiodocarbonyl > dibromocarbonyl > bromochlorocarbonyl > dichlorocarbonyl. Consistent with this suggestion is the observation that the rate of metabolism of trihalomethanes to carbon monoxide in vivo (Anders et al., 1978) or by rat liver microsomal fractions (Ahmed et al., 1977) followed the halide order: triiodomethane > tribromomethane >> chlorodibromomethane > bromodichloromethane ≈ chloroform. The carcinogenic potential of these compounds for liver or kidney, however, is the reverse of this order (see Table 26). One explanation for this relationship is that the cellular lifetime of intermediates, such as dibromocarbonyl, is extremely short because of their rapid reactivity with cellular nucleophiles (e.g., glutathione). Consequently, macromolecular binding to cellular constituents which might lead to neoplasm induction (e.g., DNA acylation) is reduced. Less reactive dihalocarbonyls, such as dichlorocarbonyl, may be sufficiently stable to cause such changes.

As indicated above, the metabolism of chloroform or bromodichloromethane may involve a common reactive intermediate, namely dichlorocarbonyl. Note the continuous dose response for liver carcinogenesis by these two compounds in female mice when doses are compared on a mole per kilogram basis (see Table 27). At doses nearly equal to or greater than those used in the studies of bromodichloromethane, tribromomethane was not carcinogenic for mouse liver. As discussed previously, this difference may be due to differences in reactivity of the dihalocarbonyl intermediates. Similarly, tribromomethane was not carcinogenic for the liver of female mice at doses higher than those at which chlorodibromomethane produced hepatocellular neoplasms. Although doses of triiodomethane were generally lower than those of the other trihalomethanes, the lack of a carcinogenic response by this compound may also be due to the high reactivity of the diiodocarbonyl intermediate with glutathione or other cellular nucleophiles. Species, sex, and target organ specificity for trihalomethane toxicity or carcinogenicity may be related to the disposition of the compound, the activities of the cytochrome P450-dependent mixed-function oxidase systems, and/or the concentrations of protective cytoplasmic nucleophiles. Trihalomethanes are metabolized to carbon dioxide more rapidly and to a greater

extent by B6C3F$_1$ mice than by Sprague Dawley rats (Mink et al., 1986). Further experimentation is needed to evaluate these proposals concerning the mechanism of liver and kidney carcinogenicity by trihalomethanes.

Results of the present studies and those of the bromodichloromethane studies (NTP, 1987; Dunnick et al., 1987) indicate that the epithelium of the large intestine is susceptible to induction of neoplasms by trihalomethanes. A common feature of a variety of diverse compounds that have been shown to induce colon neoplasms in laboratory animals is the eventual formation of a methylating intermediate (Zedeck, 1978). For trihalomethanes, the dihalocarbonyl intermediate may be the reactive form involved in the induction of large intestine neoplasms. As suggested above for induction of renal and hepatocellular neoplasms by trihalomethanes, the selectivity of the large intestine epithelium may also be dependent on the disposition of the parent compound, the rates of activation to the dihalocarbonyl intermediate, and/or the concentrations of protective cytoplasmic nucleophiles.

Tribromomethane has been shown to be mutagenic in both in vitro and in vivo assays. Tribromomethane was mutagenic in Salmonella when tested within the closed environment of a desiccator (Simmon and Tardiff, 1978; Simmon, 1981); however, results of tests for mutagenicity in Salmonella by the plate incorporation or preincubation methods were generally negative or equivocal (Simmon et al., 1977; Rapson et al., 1980; Haworth et al., 1983; Table E1). The volatility of tribromomethane may be an important factor affecting the detection of its mutagenic activity in vitro. Bromodichloromethane and chlorodibromomethane were also mutagenic in Salmonella when tested in desiccators (Simmon and Kauhanen, 1978; Simmon and Tardiff, 1978). In an in vitro cytogenetic study of trihalomethanes in human lymphocytes, increases in SCEs were produced by tribromomethane, chlorodibromomethane, bromodichloromethane, and chloroform (Morimoto and Koizumi, 1983). In cultured CHO cells, slight increases in the frequencies of SCEs and chromosomal aberrations were observed by one of two laboratories that tested tribromomethane for the NTP (Galloway et al., 1985; Tables E3 and E4). In vivo induction of SCEs by tribromomethane has also been observed in bone marrow cells of ICR/SJ mice (Morimoto and Koizumi, 1983) and B6C3F$_1$ mice (Table E7). Furthermore, tribromomethane induced increases in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of B6C3F$_1$ mice (Table E9). Thus, genotoxicity of tribromomethane has been demonstrated in a variety of test systems, and this property may be involved in the carcinogenicity of this compound.

The experimental and tabulated data for the NTP Technical Report on tribromomethane were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of tribromomethane for male F344/N rats and *clear evidence of carcinogenic activity* for female F344/N rats, based on increased incidences of uncommon neoplasms of the large intestine. Reduced survival for male rats given 200 mg/kg tribromomethane lowered the sensitivity of this group to detect a carcinogenic response. Chemically related nonneoplastic lesions included fatty change and active chronic inflammation of the liver in male and female rats, minimal necrosis of the liver in male rats, and mixed cell foci of the liver in female rats. There was *no evidence of carcinogenic activity* for male B6C3F$_1$ mice given 50 or 100 mg/kg tribromomethane or for female B6C3F$_1$ mice given 100 or 200 mg/kg; male mice might have been able to tolerate a higher dose. Survival of the female mice was reduced, partly due to a uterovarian infection.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(50)	(50)	(50)
Adenocarcinoma			1 (2%)
Leukemia mononuclear	1 (2%)		
Polyp adenomatous			2 (4%)
Intestine small	(49)	(50)	(50)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant			2 (4%)
Lymphoid nodule, leukemia mononuclear	1 (2%)		
Liver	(50)	(50)	(50)
Hepatocellular carcinoma	1 (2%)		1 (2%)
Leukemia mononuclear	14 (28%)	9 (18%)	5 (10%)
Neoplastic nodule	4 (8%)	2 (4%)	
Mesentery	*(50)	*(50)	*(50)
Fat, leukemia mononuclear	1 (2%)		
Fat, mesothelioma malignant			1 (2%)
Pancreas	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	2 (4%)	1 (2%)
Mesothelioma malignant			2 (4%)
Acinus, adenoma	1 (2%)	3 (6%)	1 (2%)
Salivary glands	(50)	(50)	(48)
Leukemia mononuclear	1 (2%)		
Sarcoma		1 (2%)	
Schwannoma malignant			1 (2%)
Stomach	(49)	(50)	(50)
Leukemia mononuclear	4 (8%)		
Forestomach, fibrosarcoma		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	6 (12%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland	(48)	(50)	(50)
Leukemia mononuclear	6 (13%)	6 (12%)	3 (6%)
Bilateral, medulla, pheochromocytoma benign	3 (6%)	1 (2%)	2 (4%)
Medulla, pheochromocytoma benign	13 (27%)	10 (20%)	6 (12%)
Islets, pancreatic	(48)	(50)	(50)
Adenoma	4 (8%)	3 (6%)	1 (2%)
Pituitary gland	(50)	(48)	(45)
Leukemia mononuclear	3 (6%)	1 (2%)	1 (2%)
Pars distalis, adenoma	11 (22%)	10 (21%)	1 (2%)
Pars distalis, adenoma, multiple	1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(49)	(49)	(47)
Leukemia mononuclear	2 (4%)		
C-cell, adenoma	2 (4%)	1 (2%)	3 (6%)
C-cell, carcinoma			1 (2%)
Follicular cell, carcinoma		3 (6%)	2 (4%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(50)	*(50)	*(50)
Adenoma		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM			
Epididymis	(45)	(49)	(41)
Mesothelioma benign		1 (2%)	
Mesothelioma malignant			2 (5%)
Preputial gland	(41)	(38)	(34)
Adenoma	4 (10%)	3 (8%)	
Carcinoma	5 (12%)	2 (5%)	1 (3%)
Leukemia mononuclear	1 (2%)		
Bilateral, carcinoma	1 (2%)		
Prostate	(49)	(46)	(50)
Leukemia mononuclear	4 (8%)		1 (2%)
Seminal vesicle	*(50)	*(50)	*(50)
Leukemia mononuclear	2 (4%)		
Mesothelioma malignant			1 (2%)
Testes	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)		
Bilateral, interstitial cell, adenoma	33 (66%)	41 (82%)	29 (58%)
Interstitial cell, adenoma	13 (26%)	4 (8%)	8 (16%)
Tunic, mesothelioma benign	2 (4%)	1 (2%)	
Tunic, mesothelioma malignant			4 (8%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(48)
Leukemia mononuclear		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymph node	(50)	(48)	(49)
Carcinoma, metastatic, lung			1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)
Axillary, leukemia mononuclear	1 (2%)		
Lumbar, leukemia mononuclear	2 (4%)		
Mandibular, leukemia mononuclear	8 (16%)	5 (10%)	3 (6%)
Mediastinal, hepatocellular carcinoma, metastatic	1 (2%)		
Mediastinal, leukemia mononuclear	9 (18%)	5 (10%)	4 (8%)
Mediastinal, lymphoma malignant lymphocytic			1 (2%)
Mesenteric, leukemia mononuclear	6 (12%)	3 (6%)	4 (8%)
Pancreatic, leukemia mononuclear	4 (8%)		1 (2%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	14 (28%)	9 (18%)	5 (10%)
Mesothelioma malignant			1 (2%)
Thymus	(47)	(46)	(41)
Leukemia mononuclear	5 (11%)	1 (2%)	2 (5%)
INTEGUMENTARY SYSTEM			
Mammary gland	(20)	(15)	(19)
Fibroadenoma	4 (20%)		
Fibroadenoma, multiple	1 (5%)	1 (7%)	
Skin	(49)	(49)	(50)
Basosquamous tumor benign	2 (4%)		
Keratoacanthoma	1 (2%)		
Squamous cell carcinoma	1 (2%)	1 (2%)	
Sebaceous gland, adenoma		1 (2%)	
Subcutaneous tissue, fibroma	4 (8%)	4 (8%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, osteosarcoma	1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Hepatocellular carcinoma, metastatic	1 (2%)		
Mesothelioma malignant			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)	
Leukemia mononuclear	5 (10%)	2 (4%)	2 (4%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)
Carcinoma			1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)
Hepatocellular carcinoma, metastatic	1 (2%)		
Leukemia mononuclear	12 (24%)	8 (16%)	4 (8%)
Lymphoma malignant lymphocytic			1 (2%)
Squamous cell carcinoma, multiple	1 (2%)		
Nose	(45)	(46)	(38)
Carcinoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Squamous cell carcinoma, metastatic, skin	1 (2%)		
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma		1 (2%)	
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	9 (18%)	6 (12%)	4 (8%)
Renal tubule, adenocarcinoma			1 (2%)
Renal tubule, adenoma	1 (2%)		
Urinary bladder	(48)	(49)	(50)
Leukemia mononuclear	3 (6%)		
Mesothelioma malignant			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	14 (28%)	9 (18%)	5 (10%)
Mesothelioma benign	2 (4%)	1 (2%)	
Mesothelioma malignant			4 (8%)
Lymphoma malignant lymphocytic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	34	30	11
Natural death	9	3	6
Moribund sacrifice	7	17	33

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	49	42
Total primary neoplasms	130	112	75
Total animals with benign neoplasms	46	47	38
Total benign neoplasms	104	91	55
Total animals with malignant neoplasms	25	21	14
Total malignant neoplasms	26	22	20
Total animals with secondary neoplasms ***	2		2
Total secondary neoplasms	4		3

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: VEHICLE CONTROL

WEEKS ON STUDY	029	054	062	069	071	074	075	083	084	088	088	089	091	094	097	099	106	106	106	106	106	106	106	106
CARCASS ID	03434	03844	03922	01012	05152	09095	06202	02222	08081	05505	01313	07474	06063	08083	07373	09094	02121	02424	02525	03303	01414	03031	03232	03505	04041
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Lymphoid nodule, leukemia mononuclear									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X										
Leukemia mononuclear				X			X		X	X				X			X		X	X				
Neoplastic nodule										X							X								
Mesentery							+									+							+		
Fat, leukemia mononuclear							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X							X						X					
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
Stomach	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X				X						X					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X					X	X										X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X					X	X				X						X					
Bilateral, medulla, pheochromocytoma benign																	X								
Medulla, pheochromocytoma benign											X	X	X							X		X		X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	M	M	+	M	M	+	M	M	M	M	+	M	M	M	+	M	+	+	+	M	M	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X	X										X					
Pars distalis, adenoma									X	X		X							X		X			X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X																		
C cell, adenoma																X									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	M	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	–	+	–	–	–	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Adenoma																									
Carcinoma		X																							
Leukemia mononuclear										X															
Bilateral, carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear							X		X	X										X					
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X													X					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X										X					
Bilateral, interstitial cell, adenoma						X	X		X				X	X				X	X	X		X	X		X
Interstitial cell, adenoma			X		X					X	X	X			X	X	X				X			X	
Tunic, mesothelioma benign																									

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A: Autolysis precludes examination
X Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL.
CARCASS ID	042	043	044	045	011	015	023	051	053	054	061	064	065	071	072	075	082	085	091	093	101	102	103	104	105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Lymphoid nodule, leukemia monuc																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear									X			X		X									X	X	X	14
Neoplastic nodule					X							X														4
Mesentery											+															4
Fat, leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Acinus, adenoma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										4
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X											X		X	7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	48
Leukemia mononuclear												X														6
Bilateral, medulla, pheochromocytoma benign					X							X														3
Medulla, pheochromocytoma benign		X					X				X				X			X				X		X		13
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Adenoma									X					X											X	4
Parathyroid gland	+	M	M	M	M	+	+	M	M	M	M	+	+	+	+	+	M	M	+	M	M	M	M	+	M	20
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Pars distalis, adenoma			X	X						X	X													X		11
Pars distalis, adenoma, multiple					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
C cell, adenoma																X										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	41
Adenoma																				X			X	X	X	4
Carcinoma		X				X			X								X									5
Leukemia mononuclear																										1
Bilateral, carcinoma																						X				1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										4
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
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	33
Interstitial cell, adenoma											X						X							X		13
Tunic, mesothelioma benign	X												X													2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	029	054	062	069	071	074	075	083	084	088	088	089	091	094	097	099	106	106	106	106	106	106	106	106
CARCASS ID	034	084	092	012	052	095	062	022	081	055	013	074	063	083	073	094	021	024	025	033	014	031	032	035	041
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, leukemia mononuclear														X											
Lumbar, leukemia mononuclear										X				X											
Mandibular, leukemia mononuclear				X			X		X	X				X			X			X					
Mediastinal, hepatocellular carcinoma, metastatic															X										
Mediastinal, leukemia mononuclear							X		X	X				X			X			X					
Mesenteric, leukemia mononuclear							X		X	X				X			X			X					
Pancreatic, leukemia mononuclear									X	X				X						X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X	X				X			X		X	X					
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X	X										X					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	+	M	+	+	M	+	+	M	M	M	M	+	+	M	+	M	+	M	M	M	+	+
Fibroadenoma																		X							X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																								X	
Keratoacanthoma																									
Squamous cell carcinoma											X														
Subcutaneous tissue, fibroma						X																X			
Subcutaneous tissue, osteosarcoma													X												
Subcutaneous tissue, sarcoma																X									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+	+									
Hepatocellular carcinoma, metastatic															X										
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X				X			X			X					
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic															X										
Leukemia mononuclear				X			X		X	X				X			X			X					
Squamous cell carcinoma, multiple								X																	
Nose	–	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Squamous cell carcinoma, metastatic, skin											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Zymbal gland																		+							
Carcinoma																		X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X	X				X			X			X					
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X													X					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	042	043	044	045	011	015	023	051	053	054	061	064	065	071	072	075	082	085	091	093	101	102	103	104	105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, leukemia mononuclear																										1
Lumbar, leukemia mononuclear																										2
Mandibular, leukemia mononuclear												X														8
Mediastinal, hepatocellular carcinoma, metastatic																										1
Mediastinal, leukemia mononuclear									X			X											X			9
Mesenteric, leukemia mononuclear																										6
Pancreatic, leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X			X		X									X	X	X	14
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Leukemia mononuclear												X														5
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	+	M	+	+	M	M	M	M	M	M	M	+	M	M	M	+	M	+	+	+	20
Fibroadenoma																	X								X	4
Fibroadenoma, multiple																					X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Basosquamous tumor benign																		X								2
Keratoacanthoma			X																							1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma							X										X									4
Subcutaneous tissue, osteosarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Hepatocellular carcinoma, metastatic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Leukemia mononuclear									X			X		X									X		X	12
Squamous cell carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																										1
Squamous cell carcinoma, metastatic, skin																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X													X	9
Renal tubule, adenoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear												X														3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: LOW DOSE

WEEKS ON STUDY	049	077	086	087	089	089	090	091	092	093	093	095	095	095	097	098	100	102	102	103	105	105	105	105
CARCASS ID	184	191	122	204	192	111	112	205	182	151	165	193	145	161	172	121	183	131	195	153	113	114	115	123	124
ALIMENTARY SYSTEM																									
Esophagus	+	M	M	M	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X		X				X		X				X					X		
Neoplastic nodule												X													
Mesentery		+			+													+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X																	
Acinus, adenoma																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, fibrosarcoma										X															
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X		X				X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X			X				X		X				X							
Bilateral, medulla, pheochromocytoma benign																							X		
Medulla, pheochromocytoma benign					X						X				X	X	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	M	+	+	+	M	+	M	M	+	+	M	M	M	M	+	M	M	+	M	+	+	+	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Pars distalis, adenoma		X			X		X	X			X					X									
Pars distalis, adenoma, multiple																					X				
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, carcinoma																				X					
GENERAL BODY SYSTEM																									
Tissue, NOS																									
Adenoma																									
GENITAL SYSTEM																									
Epididymis	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma benign																									
Preputial gland		+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X			X	X	X	X	X	X	X			X	X	X	X	X		X	X	
Interstitial cell, adenoma		X													X										X
Tunic, mesothelioma benign																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	125	132	133	134	135	141	142	144	143	152	154	155	162	163	164	171	173	174	175	181	185	194	201	202	203	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	M	M	+	+	+	M	+	+		+	+	+	+	+	+	+	+	M	M	M	36
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										9
Neoplastic nodule																								X		2
Mesentery																							+			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Acinus, adenoma			X													X										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, fibrosarcoma																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
Bilateral, medulla, pheochromocytoma benign																										1
Medulla, pheochromocytoma benign	X				X				X						X						X					10
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																				X				3
Parathyroid gland	+	M	M	M	+	M	+	M	M	+	M	M	M	+	M	M	+	M	+	M	M	M	+	M	+	20
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	48
Leukemia mononuclear																										1
Pars distalis, adenoma		X												X					X				X		10
Pars distalis, adenoma, multiple									X																	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X																									1
Follicular cell, carcinoma				X															X							3
GENERAL BODY SYSTEM																										
Tissue, NOS								+																		1
Adenoma								X																		1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma benign																						X				1
Preputial gland	+	M	+	M	M	+	+	M	M	+	M	+	M	+	+	+	M	+	+	M	+	+	+	+	+	38
Adenoma														X		X										3
Carcinoma										X																2
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	41
Interstitial cell, adenoma						X																				4
Tunic, mesothelioma benign																						X				1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	049	077	086	087	089	089	090	091	092	093	093	095	095	095	097	098	100	102	102	103	105	105	105	105	105
CARCASS ID	184	191	122	204	192	111	112	205	182	151	165	193	145	161	172	121	183	131	195	153	113	114	115	123	124
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear			X	X	X	X						X													
Mediastinal, leukemia mononuclear			X	X	X	X		X																	
Mesenteric, leukemia mononuclear			X	X		X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X		X				X		X				X					X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	M	M	+	M	M	M	+	M	+	M	M	+	M	+	M	M	+	M	+	M	M	+
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																					X				
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Leukemia mononuclear				X	X																				
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																						
Leukemia mononuclear			X	X	X	X		X				X		X									X		
Nose	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																							+		
Adenoma																									
Zymbal gland											+														
Carcinoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X			X				X						X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	125	132	133	134	135	141	142	144	143	152	154	155	162	163	164	171	173	174	175	181	185	194	201	202	203	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	48
Mandibular, leukemia mononuclear																										5
Mediastinal, leukemia mononuclear																										5
Mesenteric, leukemia mononuclear																										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										9
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	46
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	+	+	+	M	M	+	M	15
Fibroadenoma, multiple								X																		1
Skin	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Sebaceous gland, adenoma																									X	1
Subcutaneous tissue, fibroma	X														X	X									X	4
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Leukemia mononuclear																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Leukemia mononuclear																										8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	46
Carcinoma					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye						+																				1
Harderian gland					+	+																				3
Adenoma					X																					1
Zymbal gland									+																	2
Carcinoma									X																	2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: HIGH DOSE

WEEKS ON STUDY	033	034	036	040	043	044	044	051	052	057	072	076	077	085	086	086	087	088	091	092	092	092	092	092
CARCASS ID	292	232	284	253	221	224	225	245	282	295	291	241	264	233	261	305	304	235	303	234	272	213	243	281	215
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	M	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous												X													
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																			X						
Leukemia mononuclear															X				X						
Mesentery								+																	
Fat, mesothelioma malignant								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant								X																	
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Bilateral, medulla, pheochromocytoma benign																									
Medulla, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	M	M	M	M	+	+	M	+	M	M	+	M	M	+	+	+	M	M	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Leukemia mononuclear																			X						
Pars distalis, adenoma																		X							
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
C-cell, carcinoma																									X
Follicular cell, carcinoma															X										X
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	–	–	–	–	M	M	M	–	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																									X
Preputial gland	–	–	–	–	–	–	–	–	–	–	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant								X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma														X		X		X			X	X		X	X
Interstitial cell, adenoma											X		X				X			X			X		
Tunic, mesothelioma malignant								X											X						X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	092	093	093	095	095	096	096	096	096	099	102	103	103	104	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	242	214	244	223	275	222	255	262	231	263	301	252	302	271	211	212	251	254	265	273	274	283	285	293	294	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma														X												1
Polyp adenomatous																						X				2
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant									X																	2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Leukemia mononuclear										X							X		X							5
Mesentery							+																	+		3
Fat, mesothelioma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X																1
Mesothelioma malignant									X																	2
Acinus, adenoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Schwannoma malignant			X																							1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X							X									2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X							X									3
Bilateral, medulla, pheochromocytoma benign						X																	X			2
Medulla, pheochromocytoma benign									X			X						X	X		X					6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Parathyroid gland	M	M	M	M	+	M	+	M	+	+	+	M	M	M	M	+	M	M	M	M	M	+	+	M	M	18
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																										1
Pars distalis, adenoma																										1
Pars distalis, adenoma, multiple																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	47
C-cell, adenoma			X								X															3
C-cell, carcinoma																										1
Follicular cell, carcinoma																										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Mesothelioma malignant									X																	2
Preputial gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	34
Carcinoma													X													1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X																1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	29
Interstitial cell, adenoma		X											X			X										8
Tunic, mesothelioma malignant									X																	4

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	033	034	036	040	043	044	044	051	052	057	072	076	077	085	086	086	087	088	091	092	092	092	092	092
CARCASS ID	292	232	284	253	221	224	225	245	282	295	291	241	264	233	261	305	304	235	303	234	272	213	243	281	215
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Leukemia mononuclear																									
Lymphoma malignant lymphocytic										X															
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									X
Carcinoma, metastatic, lung														X											
Mandibular, leukemia mononuclear															X										
Mediastinal, leukemia mononuclear															X				X						
Mediastinal, lymphoma malignant lymphocytic										X															
Mesenteric, leukemia mononuclear															X				X						
Pancreatic, leukemia mononuclear																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X				X						
Mesothelioma malignant								X																	
Thymus	+	+	+	+	M	M	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	M	M	M	M	+	+	M	+	+	+	M	M	M	+	M	M	M	M	+	+	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Mesothelioma malignant																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma														X											
Carcinoma, metastatic, thyroid gland																									X
Leukemia mononuclear															X				X						
Lymphoma malignant lymphocytic										X															
Nose	–	–	–	–	–	–	–	–	–	–	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland											+														
Zymbal gland												+													
Carcinoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X				X						
Renal tubule, adenocarcinoma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	092	093	093	095	095	096	096	096	096	099	102	103	103	104	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	242	214	244	223	275	222	255	262	231	263	301	252	302	271	211	212	251	254	265	273	274	283	285	293	294	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear										X																1
Lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																										1
Carcinoma, metastatic, lung																										1
Mandibular, leukemia mononuclear										X							X									3
Mediastinal, leukemia mononuclear										X							X									4
Mediastinal, lymphoma malignant lymphocytic																										1
Mesenteric, leukemia mononuclear										X							X									4
Pancreatic, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X							X		X							5
Mesothelioma malignant																										1
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	41
Leukemia mononuclear																	X									2
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	M	M	+	M	M	+	+	M	+	M	M	+	M	M	+	+	M	M	M	M	M	M	19
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle									+																	1
Mesothelioma malignant									X																	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X																2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										1
Carcinoma																										1
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear										X							X									4
Lymphoma malignant lymphocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																			+							2
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X							X									4
Renal tubule, adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant									X																	1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	16/48 (33%)	11/50 (22%)	8/50 (16%)
Adjusted Rates (b)	45.1%	30.0%	49.2%
Terminal Rates (c)	13/32 (41%)	6/30 (20%)	4/11 (36%)
Day of First Observation	611	621	643
Life Table Tests (d)	P=0.510	P=0.209N	P=0.415
Logistic Regression Tests (d)	P=0.132N	P=0.110N	P=0.245N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.152N	P=0.039N
Preputial Gland: Adenoma			
Overall Rates (a)	4/41 (10%)	3/38 (8%)	0/34 (0%)
Adjusted Rates (b)	13.3%	11.6%	0.0%
Terminal Rates (c)	4/30 (13%)	2/21 (10%)	0/10 (0%)
Day of First Observation	734	632	
Life Table Tests (d)	P=0.219N	P=0.655N	P=0.274N
Logistic Regression Tests (d)	P=0.118N	P=0.573N	P=0.270N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.543N	P=0.083N
Preputial Gland: Carcinoma			
Overall Rates (a)	6/41 (15%)	2/38 (5%)	1/34 (3%)
Adjusted Rates (b)	18.4%	7.5%	7.7%
Terminal Rates (c)	5/30 (17%)	1/21 (5%)	0/10 (0%)
Day of First Observation	377	680	716
Life Table Tests (d)	P=0.181N	P=0.235N	P=0.336N
Logistic Regression Tests (d)	P=0.042N	P=0.160N	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.046N		
Fisher Exact Test (d)		P=0.158N	P=0.088N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	10/41 (24%)	5/38 (13%)	1/34 (3%)
Adjusted Rates (b)	31.4%	18.7%	7.7%
Terminal Rates (c)	9/30 (30%)	3/21 (14%)	0/10 (0%)
Day of First Observation	377	632	716
Life Table Tests (d)	P=0.077N	P=0.288N	P=0.134N
Logistic Regression Tests (d)	P=0.008N	P=0.163N	P=0.014N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.163N	P=0.008N
Pancreatic Islets: Adenoma			
Overall Rates (a)	4/48 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	12.5%	9.3%	5.3%
Terminal Rates (c)	4/32 (13%)	2/30 (7%)	0/11 (0%)
Day of First Observation	734	679	670
Life Table Tests (d)	P=0.428N	P=0.530N	P=0.554N
Logistic Regression Tests (d)	P=0.251N	P=0.464N	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.477N	P=0.168N
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	11.0%	5.8%	0.0%
Terminal Rates (c)	3/34 (9%)	1/30 (3%)	0/11 (0%)
Day of First Observation	610	659	
Life Table Tests (d)	P=0.122N	P=0.362N	P=0.220N
Logistic Regression Tests (d)	P=0.054N	P=0.320N	P=0.109N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.339N	P=0.059N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Large Intestine: Adenomatous Polyp or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	18.8%
Terminal Rates (c)	0/34 (0%)	0/30 (0%)	1/11 (9%)
Day of First Observation			527
Life Table Tests (d)	P=0.008	(e)	P=0.028
Logistic Regression Tests (d)	P=0.030	(e)	P=0.092
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(e)	P=0.121
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	13.5%	5.8%	3.1%
Terminal Rates (c)	3/34 (9%)	1/30 (3%)	0/11 (0%)
Day of First Observation	610	659	636
Life Table Tests (d)	P=0.194N	P=0.239N	P=0.343N
Logistic Regression Tests (d)	P=0.082N	P=0.204N	P=0.161N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.218N	P=0.102N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	14.7%	3.3%	0.0%
Terminal Rates (c)	5/34 (15%)	1/30 (3%)	0/11 (0%)
Day of First Observation	734	734	
Life Table Tests (d)	P=0.057N	P=0.132N	P=0.215N
Logistic Regression Tests (d)	P=0.057N	P=0.132N	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.102N	P=0.028N
Pancreas: Acinar Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.9%	10.0%	5.0%
Terminal Rates (c)	1/34 (3%)	3/30 (10%)	0/11 (0%)
Day of First Observation	734	734	666
Life Table Tests (d)	P=0.285	P=0.261	P=0.563
Logistic Regression Tests (d)	P=0.417	P=0.261	P=0.691
Cochran-Armitage Trend Test (d)	P=0.610N		
Fisher Exact Test (d)		P=0.309	P=0.753N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	12/50 (24%)	12/48 (25%)	2/45 (4%)
Adjusted Rates (b)	31.8%	31.9%	11.8%
Terminal Rates (c)	9/34 (26%)	6/28 (21%)	1/11 (9%)
Day of First Observation	586	537	616
Life Table Tests (d)	P=0.149N	P=0.508	P=0.130N
Logistic Regression Tests (d)	P=0.024N	P=0.567	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.547	P=0.007N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	10.8%	13.3%	0.0%
Terminal Rates (c)	3/34 (9%)	4/30 (13%)	0/11 (0%)
Day of First Observation	514	734	
Life Table Tests (d)	P=0.253N	P=0.589	P=0.214N
Logistic Regression Tests (d)	P=0.103N	P=0.620N	P=0.084N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.643N	P=0.059N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	13.4%	15.6%	0.0%
Terminal Rates (c)	3/34 (9%)	4/30 (13%)	0/11 (0%)
Day of First Observation	514	659	
Life Table Tests (d)	P=0.195N	P=0.582	P=0.158N
Logistic Regression Tests (d)	P=0.061N	P=0.609N	P=0.048N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.630N	P=0.028N
Testis: Adenoma			
Overall Rates (a)	46/50 (92%)	45/50 (90%)	37/50 (74%)
Adjusted Rates (b)	100.0%	97.8%	100.0%
Terminal Rates (c)	34/34 (100%)	29/30 (97%)	11/11 (100%)
Day of First Observation	429	537	499
Life Table Tests (d)	P<0.001	P=0.432	P<0.001
Logistic Regression Tests (d)	P=0.234N	P=0.134N	P=0.250N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.500N	P=0.016N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/49 (4%)	1/49 (2%)	3/47 (6%)
Adjusted Rates (b)	5.7%	3.3%	13.2%
Terminal Rates (c)	1/34 (3%)	1/30 (3%)	0/9 (0%)
Day of First Observation	688	734	603
Life Table Tests (d)	P=0.152	P=0.532N	P=0.209
Logistic Regression Tests (d)	P=0.303	P=0.488N	P=0.383
Cochran-Armitage Trend Test (d)	P=0.383		
Fisher Exact Test (d)		P=0.500N	P=0.480
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	1/49 (2%)	4/47 (9%)
Adjusted Rates (b)	5.7%	3.3%	16.5%
Terminal Rates (c)	1/34 (3%)	1/30 (3%)	0/9 (0%)
Day of First Observation	688	734	603
Life Table Tests (d)	P=0.065	P=0.532N	P=0.107
Logistic Regression Tests (d)	P=0.166	P=0.488N	P=0.233
Cochran-Armitage Trend Test (d)	P=0.224		
Fisher Exact Test (d)		P=0.500N	P=0.319
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	3/49 (6%)	2/47 (4%)
Adjusted Rates (b)	0.0%	9.7%	6.5%
Terminal Rates (c)	0/34 (0%)	2/30 (7%)	0/9 (0%)
Day of First Observation		721	600
Life Table Tests (d)	P=0.054	P=0.103	P=0.188
Logistic Regression Tests (d)	P=0.134	P=0.114	P=0.229
Cochran-Armitage Trend Test (d)	P=0.190		
Fisher Exact Test (d)		P=0.121	P=0.237
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	14/50 (28%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	34.8%	20.4%	27.8%
Terminal Rates (c)	9/34 (26%)	1/30 (3%)	2/11 (18%)
Day of First Observation	483	600	600
Life Table Tests (d)	P=0.190N	P=0.193N	P=0.364N
Logistic Regression Tests (d)	P=0.019N	P=0.200N	P=0.048N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.171N	P=0.020N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
All Sites: All Mesothelioma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	5.9%	3.3%	14.4%
Terminal Rates (c)	2/34 (6%)	1/30 (3%)	0/11 (0%)
Day of First Observation	734	734	356
Life Table Tests (d)	P=0.076	P=0.544N	P=0.121
Logistic Regression Tests (d)	P=0.247	P=0.544N	P=0.337
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.

TABLE A4a. HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
TOTAL	0/285
Overall Historical Incidence	
TOTAL	(b) 3/1,873 (0.2%)

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Includes one adenomatous polyp, NOS, one cystadenoma, NOS, and one adenocarcinoma, NOS

TABLE A4b. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	0/50	1/50	1/50
Diglycidyl resorcinol ether	1/50	(b) 2/50	(b) 3/50
1,2-Dichloropropane	0/50	(b) 2/50	(b) 2/50
Chlorodibromomethane	1/50	0/50	1/50
n-Butyl chloride	1/50	2/50	3/50
Bromodichloromethane	0/50	2/50	2/50
TOTAL	3/300 (1.0%)	9/300 (3.0%)	12/300 (4.0%)
SD (c)	1.10%	1.67%	1.79%
Range (d)			
High	1/50	2/50	3/50
Low	0/50	0/50	1/50
Overall Historical Incidence			
TOTAL	37/1,949 (1.9%)	(e) 42/1,949 (2.2%)	(e) 79/1,949 (4.1%)
SD (c)	3.01%	2.36%	3.93%
Range (d)			
High	7/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Includes one squamous cell carcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes three squamous cell carcinomas and seven adenocarcinomas, NOS

TABLE A4c. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	5/50
Diglycidyl resorcinol ether	6/50
1,2-Dichloropropane	8/50
Chlorodibromomethane	6/50
n-Butyl chloride	11/50
Bromodichloromethane	8/50
TOTAL	44/300 (14.7%)
SD (b)	4.32%
Range (c)	
High	11/50
Low	5/50
Overall Historical Incidence	
TOTAL	321/1,949 (16.5%)
SD (b)	8.95%
Range (c)	
High	22/50
Low	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	17/49	0/49	17/49
Diglycidyl resorcinol ether	17/50	0/50	17/50
1,2-Dichloropropane	19/50	3/50	22/50
Chlorodibromomethane	12/49	3/49	15/49
n-Butyl chloride	18/48	1/48	19/48
Bromodichloromethane	13/48	4/48	17/48
TOTAL	96/294 (32.7%)	11/294 (3.7%)	107/294 (36.4%)
SD (b)	5.58%	3.54%	4.71%
Range (c)			
High	19/50	4/48	22/50
Low	12/49	0/50	15/49
Overall Historical Incidence			
TOTAL	(d) 519/1,898 (27.3%)	(e) 38/1,898 (2.0%)	(d,e) 556/1,898 (29.3%)
SD (b)	10.31%	2.61%	10.48%
Range (c)			
High	26/48	4/47	26/48
Low	5/50	0/50	6/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 34 chromophobe adenomas and 1 acidophil adenoma
(e) Includes four chromophobe carcinomas and three adenocarcinomas, NOS

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(50)	(50)	(50)
Abscess	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Parasite	2 (4%)	5 (10%)	5 (10%)
Cecum, inflammation, chronic active	1 (2%)		
Colon, erosion			1 (2%)
Colon, hyperplasia, lymphoid	1 (2%)		
Lymphoid nodule, hyperplasia		1 (2%)	1 (2%)
Intestine small	(49)	(50)	(50)
Ileum, fibrosis			1 (2%)
Ileum, necrosis			1 (2%)
Liver	(50)	(50)	(50)
Basophilic focus	28 (56%)	20 (40%)	24 (48%)
Clear cell focus		2 (4%)	
Degeneration, cystic		1 (2%)	
Eosinophilic focus	1 (2%)	9 (18%)	4 (8%)
Fatty change, diffuse	5 (10%)	13 (26%)	27 (54%)
Fatty change, focal	18 (36%)	36 (72%)	23 (46%)
Focal cellular change		1 (2%)	
Hepatodiaphragmatic nodule		1 (2%)	
Hyperplasia, focal	2 (4%)	1 (2%)	
Hyperplasia, multifocal	2 (4%)	2 (4%)	
Inflammation, chronic active		29 (58%)	23 (46%)
Mixed cell focus	10 (20%)	11 (22%)	8 (16%)
Necrosis	7 (14%)	3 (6%)	20 (40%)
Bile duct, hyperplasia	39 (78%)	37 (74%)	22 (44%)
Mesentery	(4)	(4)	(3)
Artery, necrosis, fibrinoid	1 (25%)		
Fat, inflammation, chronic active	1 (25%)	1 (25%)	
Fat, necrosis	2 (50%)	3 (75%)	1 (33%)
Pancreas	(50)	(50)	(50)
Acinus, atrophy	6 (12%)	9 (18%)	3 (6%)
Acinus, hyperplasia	4 (8%)	2 (4%)	3 (6%)
Artery, necrosis, fibrinoid	1 (2%)		
Artery, thrombus			1 (2%)
Salivary glands	(50)	(50)	(48)
Atrophy		1 (2%)	1 (2%)
Atrophy, focal	1 (2%)	1 (2%)	
Fibrosis		1 (2%)	1 (2%)
Inflammation, chronic active		2 (4%)	3 (6%)
Duct, ectasia		5 (10%)	
Duct, inflammation, chronic active		14 (28%)	22 (46%)
Duct, metaplasia, squamous		15 (30%)	31 (65%)
Stomach	(49)	(50)	(50)
Forestomach, acanthosis	1 (2%)	1 (2%)	
Forestomach, fibrosis		2 (4%)	
Forestomach, hyperkeratosis	6 (12%)	8 (16%)	4 (8%)
Forestomach, hyperplasia, basal cell			3 (6%)
Forestomach, inflammation, chronic active	4 (8%)	4 (8%)	10 (20%)
Forestomach, necrosis	3 (6%)		
Forestomach, ulcer	1 (2%)	5 (10%)	10 (20%)
Glandular, necrosis			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Cardiomyopathy	42 (84%)	39 (78%)	23 (46%)
ENDOCRINE SYSTEM			
Adrenal gland	(48)	(50)	(50)
Cyst		2 (4%)	
Thrombus	1 (2%)		
Cortex, hyperplasia	3 (6%)	1 (2%)	
Cortex, hypertrophy, focal			1 (2%)
Cortex, necrosis	1 (2%)	1 (2%)	1 (2%)
Medulla, hyperplasia	21 (44%)	16 (32%)	6 (12%)
Islets, pancreatic	(48)	(50)	(50)
Hyperplasia	2 (4%)	3 (6%)	2 (4%)
Pituitary gland	(50)	(48)	(45)
Pars distalis, angiectasis	11 (22%)	12 (25%)	1 (2%)
Pars distalis, cyst	2 (4%)	2 (4%)	
Pars distalis, hyperplasia	9 (18%)	26 (54%)	15 (33%)
Pars intermedia, hyperplasia	2 (4%)		
Pars nervosa, cyst	1 (2%)		1 (2%)
Thyroid gland	(49)	(49)	(47)
Mineralization			1 (2%)
Necrosis			1 (2%)
C-cell, hyperplasia	3 (6%)	3 (6%)	
Capsule, necrosis, fibrinoid	1 (2%)		
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(45)	(49)	(41)
Inflammation, chronic active			1 (2%)
Preputial gland	(41)	(38)	(34)
Fibrosis	2 (5%)		
Inflammation, chronic active	7 (17%)	11 (29%)	10 (29%)
Mineralization	1 (2%)		
Necrosis	7 (17%)	3 (8%)	7 (21%)
Prostate	(49)	(46)	(50)
Fibrosis	2 (4%)	4 (9%)	5 (10%)
Inflammation, acute	1 (2%)		
Inflammation, chronic active	16 (33%)	17 (37%)	19 (38%)
Metaplasia, squamous	2 (4%)	6 (13%)	12 (24%)
Mineralization		1 (2%)	1 (2%)
Epithelium, hyperplasia	1 (2%)	2 (4%)	3 (6%)
Seminal vesicle	(50)	(48)	(50)
Atrophy	1 (2%)		
Inflammation			1 (2%)
Testes	(50)	(50)	(50)
Spermatocele		1 (2%)	1 (2%)
Interstitial cell, hyperplasia	37 (74%)	39 (78%)	39 (78%)
Seminiferous tubule, atrophy	40 (80%)	38 (76%)	33 (66%)
Seminiferous tubule, giant cell		6 (12%)	1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(48)	(49)
Lumbar, pigmentation	1 (2%)		1 (2%)
Mandibular, infiltration cellular, plasma cell		4 (8%)	
Mandibular, necrosis		1 (2%)	
Mediastinal, angiectasis	2 (4%)		3 (6%)
Mediastinal, congestion		1 (2%)	1 (2%)
Mediastinal, depletion lymphoid		1 (2%)	1 (2%)
Mediastinal, hemorrhage	1 (2%)		1 (2%)
Mediastinal, pigmentation	2 (4%)		12 (24%)
Mesenteric, angiectasis	1 (2%)		
Mesenteric, infiltration cellular, mast cell			2 (4%)
Pancreatic, angiectasis	1 (2%)		
Pancreatic, pigmentation			1 (2%)
Spleen	(50)	(50)	(50)
Cyst		1 (2%)	
Depletion lymphoid			4 (8%)
Fibrosis		2 (4%)	
Hematopoietic cell proliferation	30 (60%)	36 (72%)	35 (70%)
Infarct			1 (2%)
Pigmentation	1 (2%)	2 (4%)	
Thymus	(47)	(46)	(41)
Epithelial cell, hyperplasia	2 (4%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(20)	(15)	(19)
Galactocele	1 (5%)		
Skin	(49)	(49)	(50)
Acanthosis	1 (2%)		
Cyst		1 (2%)	
Cyst epithelial inclusion	1 (2%)		
Hemorrhage			1 (2%)
Hyperkeratosis	2 (4%)	1 (2%)	
Inflammation, chronic active		3 (6%)	
Necrosis	2 (4%)		2 (4%)
Subcutaneous tissue, necrosis		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(49)
Joint, tarsal, hyperostosis	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Hemorrhage		2 (4%)	
Artery, thrombus		1 (2%)	
Brain stem, vacuolization cytoplasmic			2 (4%)
White matter, cerebrum, vacuolization cytoplasmic			2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Bronchiectasis	1 (2%)		1 (2%)
Edema	2 (4%)	3 (6%)	
Infiltration cellular, histiocytic	8 (16%)	9 (18%)	13 (26%)
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic active	1 (2%)	7 (14%)	15 (30%)
Inflammation, granulomatous			1 (2%)
Mineralization		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	6 (12%)	4 (8%)
Bronchiole, inflammation, acute			3 (6%)
Bronchus, metaplasia, squamous			1 (2%)
Nose	(45)	(46)	(38)
Inflammation, chronic active	1 (2%)	3 (7%)	4 (11%)
Metaplasia, squamous			1 (3%)
Nasolacrimal duct, inflammation			1 (3%)
SPECIAL SENSES SYSTEM			
Harderian gland		(3)	(2)
Hyperplasia		1 (33%)	
Inflammation, chronic active			1 (50%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)
Fibrosis			1 (2%)
Fibrosis, focal		1 (2%)	
Hydronephrosis	1 (2%)		1 (2%)
Necrosis			2 (4%)
Nephropathy	46 (92%)	50 (100%)	45 (90%)
Artery, necrosis, fibrinoid			1 (2%)
Pelvis, inflammation, acute			1 (2%)
Renal tubule, degeneration			1 (2%)
Transitional epithelium, hyperplasia			1 (2%)
Urinary bladder	(48)	(49)	(50)
Hemorrhage	3 (6%)		2 (4%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)
Necrosis	1 (2%)		3 (6%)
Transitional epithelium, hyperplasia	1 (2%)		3 (6%)

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)	*(50)	(49)
Adenocarcinoma			2 (4%)
Leukemia mononuclear	1 (2%)		
Polyp adenomatous		1 (2%)	6 (12%)
Intestine small	(48)	*(50)	(49)
Leukemia mononuclear	1 (2%)		
Liver	(50)	(49)	(50)
Leukemia mononuclear	9 (18%)	13 (27%)	6 (12%)
Lymphoma malignant histiocytic	1 (2%)		
Neoplastic nodule		4 (8%)	1 (2%)
Neoplastic nodule, multiple			1 (2%)
Pancreas	(48)	(49)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Acinus, adenoma	1 (2%)		2 (4%)
Acinus, adenoma, multiple			1 (2%)
Acinus, carcinoma		1 (2%)	
Salivary glands	(49)	(49)	(50)
Leukemia mononuclear	1 (2%)		
Stomach	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)		1 (2%)
Forestomach, papilloma squamous	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	7 (14%)	2 (4%)	4 (8%)
Pericardium, alveolar/bronchiolar carcinoma, metastatic			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	*(50)	(50)
Leukemia mononuclear	6 (12%)	4 (8%)	2 (4%)
Medulla, pheochromocytoma benign	2 (4%)		3 (6%)
Islets, pancreatic	(48)	(49)	(50)
Adenoma	2 (4%)		
Pituitary gland	(48)	(46)	(48)
Leukemia mononuclear	3 (6%)	2 (4%)	
Pars distalis, adenoma	26 (54%)	10 (22%)	16 (33%)
Pars distalis, adenoma, multiple	3 (6%)	2 (4%)	
Thyroid gland	(50)	(47)	(49)
C-cell, adenoma	4 (8%)	3 (6%)	2 (4%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma	1 (2%)	1 (2%)	2 (4%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM			
Clitoral gland	(34)	*(50)	(39)
Adenoma		1 (2%)	2 (5%)
Carcinoma	1 (3%)	1 (2%)	
Ovary	(50)	*(50)	(50)
Granulosa cell tumor		1 (2%)	1 (2%)
Leukemia mononuclear	6 (12%)	2 (4%)	2 (4%)
Uterus	(49)	(50)	(50)
Leiomyosarcoma	1 (2%)		
Leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Polyp stromal	9 (18%)	9 (18%)	2 (4%)
Polyp stromal, multiple	1 (2%)		
Sarcoma stromal	1 (2%)		
Vagina	*(50)	*(50)	*(50)
Squamous cell carcinoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(48)	*(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Lymph node	(50)	*(50)	(49)
Axillary, leukemia mononuclear		2 (4%)	
Lumbar, leukemia mononuclear	2 (4%)		
Mandibular, leukemia mononuclear	5 (10%)	5 (10%)	1 (2%)
Mediastinal, leukemia mononuclear	4 (8%)	4 (8%)	2 (4%)
Mesenteric, leukemia mononuclear	5 (10%)	7 (14%)	2 (4%)
Pancreatic, leukemia mononuclear	2 (4%)	4 (8%)	1 (2%)
Renal, leukemia mononuclear	1 (2%)	2 (4%)	
Spleen	(49)	*(50)	(50)
Leukemia mononuclear	8 (16%)	13 (26%)	6 (12%)
Thymus	(48)	*(50)	(48)
Leukemia mononuclear	4 (8%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Epithelial cell, thymoma, NOS	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	*(50)	(39)
Adenocarcinoma, multiple	1 (2%)		
Fibroadenoma	14 (32%)	16 (32%)	6 (15%)
Fibroadenoma, multiple	8 (18%)	1 (2%)	
Leukemia mononuclear		1 (2%)	
Skin	(50)	*(50)	(50)
Subcutaneous tissue, fibrosarcoma	1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Astrocytoma malignant			1 (2%)
Leukemia mononuclear	3 (6%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Carcinoma, metastatic, clitoral gland		1 (2%)	
Leukemia mononuclear	7 (14%)	10 (20%)	5 (10%)
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	7 (14%)	3 (6%)
Sarcoma			1 (2%)
Pelvis, transitional epithelium, papilloma			1 (2%)
Renal tubule, adenoma			1 (2%)
Urinary bladder	(45)	*(50)	(46)
Leukemia mononuclear	2 (4%)		2 (4%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Leukemia mononuclear	9 (18%)	13 (26%)	6 (12%)
Lymphoma malignant histiocytic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	33	28	28
Natural death	4	6	2
Moribund sacrifice	13	16	19
Gavage death			1
TUMOR SUMMARY			
Total animals with primary neoplasms **	47	37	38
Total primary neoplasms	93	68	60
Total animals with benign neoplasms	41	28	33
Total benign neoplasms	74	49	47
Total animals with malignant neoplasms	17	18	10
Total malignant neoplasms	18	18	12
Total animals with secondary neoplasms ***		1	1
Total secondary neoplasms		1	1
Total animals with neoplasms-- uncertain benign or malignant	1	1	1
Total uncertain neoplasms	1	1	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: VEHICLE CONTROL

WEEKS ON STUDY	077	088	090	090	090	092	092	093	095	095	096	096	098	099	101	105	106	106	106	106	106	106	106	106	106
CARCASS ID	405	402	343	355	404	332	315	314	351	324	384	321	361	393	334	372	331	374	311	312	313	322	323	325	333
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X			X			X			X								X
Lymphoma malignant histiocytic																									
Mesentery						+																	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Acinus, adenoma																			X						
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Forestomach, papilloma squamous		X																							
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X			X			X			X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X						X			X								
Medulla, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	+	M	+	+	+	+	M	+	M	M	+	M	+	M	M	M	+	+	M	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Pars distalis, adenoma		X	X	X	X	X			X	X		X		X		X		X	X	X	X	X	X		
Pars distalis, adenoma, multiple																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
C-cell, carcinoma																									
Follicular cell, adenoma																								X	
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	M	M	+	+	M	+	+	+	M	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+
Carcinoma					X																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X			X						X								
Uterus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma															X										
Leukemia mononuclear																									
Polyp stromal					X							X											X		
Polyp stromal, multiple															X										
Sarcoma stromal	X																								

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	107	107	107	107	107	107	TOTAL:
CARCASS ID	335	341	342	344	345	352	353	354	362	363	364	365	371	373	375	382	385	392	401	381	383	391	394	395	403	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X													1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X													1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X				X		X											9
Lymphoma malignant histiocytic					X																					1
Mesentery											+						+									4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X													1
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear													X													1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X													2
Forestomach, papilloma squamous																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X		X											7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X		X											6
Medulla, pheochromocytoma benign					X																				X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X							X																	2
Parathyroid gland	M	+	+	M	+	M	M	+	M	M	M	M	M	M	M	M	+	+	M	M	+	+	M	M	+	21
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X		X											3
Pars distalis, adenoma	X		X	X	X			X							X	X		X					X	X		26
Pars distalis, adenoma, multiple									X		X															3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X														X							X	4
C-cell, carcinoma																			X							1
Follicular cell, adenoma																										1
Follicular cell, carcinoma					X																					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	M	+	+	M	+	M	34
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X		X											6
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Leukemia mononuclear													X													1
Polyp stromal										X				X		X		X		X				X		9
Polyp stromal, multiple																										1
Sarcoma stromal																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	07	08	09	09	09	09	09	09	09	09	09	09	09	10	10	10	10	10	10	10	10	10	10	10
CARCASS ID	405	402	343	355	404	332	315	314	351	324	384	321	361	993	334	372	331	374	311	312	313	322	323	325	333
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, leukemia mononuclear																	X								
Mandibular, leukemia mononuclear											X			X			X								
Mediastinal, leukemia mononuclear											X						X								
Mesenteric, leukemia mononuclear								X			X			X			X								
Pancreatic, leukemia mononuclear														X											
Renal, leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X			X			X			X								
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X														
Lymphoma malignant lymphocytic																					X				
Epithelial cell, thymoma, NOS							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma, multiple																									
Fibroadenoma	X	X	X		X	X						X	X						X	X					
Fibroadenoma, multiple				X																		X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X							X			X								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X					X						
Leukemia mononuclear							X	X			X			X			X								
Nose	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland								+																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X			X			X			X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	A	+	A	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	107	107	107	107	107	TOTAL:
CARCASS ID	335	341	342	344	345	352	353	354	362	363	364	365	371	373	375	382	385	392	401	381	383	391	394	395	403	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X													1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumbar, leukemia mononuclear													X													2
Mandibular, leukemia mononuclear													X		X											5
Mediastinal, leukemia mononuclear													X		X											4
Mesenteric, leukemia mononuclear													X													5
Pancreatic, leukemia mononuclear													X													2
Renal, leukemia mononuclear													X													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear								X					X		X											8
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear													X		X											4
Lymphoma malignant lymphocytic																										1
Epithelial cell, thymoma, NOS																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	44
Adenocarcinoma, multiple												X														1
Fibroadenoma			X						X										X		X			X		14
Fibroadenoma, multiple						X					X					X				X					X	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																							X			1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Leukemia mononuclear													X		X											7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X		X											7
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear													X		X											2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: LOW DOSE

WEEKS ON STUDY	007	008	019	040	049	075	077	083	083	084	087	087	089	089	090	090	092	094	097	099	099	104	105	106	106
CARCASS ID	495	472	442	411	505	504	422	455	503	475	454	482	413	465	443	485	493	473	511	414	492	434	432	412	415
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+		+		+				
Polyp adenomatous																									
Intestine small	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+						+		
Liver	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X			X	X	X		X	X		X				
Neoplastic nodule																						X	X		
Mesentery													+			+									
Pancreas	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, carcinoma																									
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+		+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leukemia mononuclear									X	X															
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+				+				
Leukemia mononuclear										X				X		X					X				
Islets, pancreatic	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	+	M	M	M	M	+	+	+	M	+	M	M	+								
Pituitary gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Leukemia mononuclear																		X			X				
Pars distalis, adenoma							X				X				X										
Pars distalis, adenoma, multiple																						X		X	
Thyroid gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X	X															
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	–	–	–	–	–	+	M	+	+	+	+	+	M	M	M	+	+								
Adenoma																									
Carcinoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+					
Granulosa cell tumor																									
Leukemia mononuclear										X				X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Polyp stromal							X	X	X													X		X	
Vagina																					+				
Squamous cell carcinoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, leukemia mononuclear									X									X							
Mandibular, leukemia mononuclear									X					X		X		X							
Mediastinal, leukemia mononuclear									X	X				X				X							
Mesenteric, leukemia mononuclear								X	X	X				X		X		X	X						
Pancreatic, leukemia mononuclear									X					X				X							
Renal, leukemia mononuclear									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+	
Leukemia mononuclear								X	X	X	X			X	X	X		X	X		X				
Thymus	+	M	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+								
Leukemia mononuclear									X																
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma													X		X			X		X		X	X	X	X
Fibroadenoma, multiple																									
Leukemia mononuclear																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma																				X					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
RESPIRATORY SYSTEM																									
Lung	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+				+		
Alveolar/bronchiolar adenoma															X										
Carcinoma, metastatic, clitoral gland																	X								
Leukemia mononuclear								X	X	X	X			X	X	X			X						
Nose	–	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+								
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																		+			+				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X				X				X			X				
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	M	M	+	+	+	+								

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	421	423	424	425	431	433	435	441	444	445	452	453	461	462	464	463	471	474	481	483	484	491	494	501	502	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large													+													18
Polyp adenomatous													X													1
Intestine small																										16
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear									X						X		X									13
Neoplastic nodule		X														X										4
Mesentery																						+				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, carcinoma																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach			+	+			+											+								26
CARDIOVASCULAR SYSTEM																										
Heart																										16
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland																									+	18
Leukemia mononuclear																										4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+		+			+	+		+						+		+	+				+			16
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear																										2
Pars distalis, adenoma			X		X			X				X						X					X		X	10
Pars distalis, adenoma, multiple																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
C-cell, adenoma			X																							3
Follicular cell, adenoma			X																							1
Follicular cell, carcinoma					X																					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																		+								9
Adenoma																		X								1
Carcinoma																										1
Ovary																								+		20
Granulosa cell tumor																								X		1
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Polyp stromal		X				X		X				X														9
Vagina		+																								2
Squamous cell carcinoma		X																								1
HEMATOPOIETIC SYSTEM																										
Bone marrow																										16
Lymph node	+	+	+	+	+	+		+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	47
Axillary, leukemia mononuclear																										2
Mandibular, leukemia mononuclear															X											5
Mediastinal, leukemia mononuclear																										4
Mesenteric, leukemia mononuclear																										7
Pancreatic, leukemia mononuclear															X											4
Renal, leukemia mononuclear															X											2
Spleen							+		+		+				+		+							+	+	28
Leukemia mononuclear									X						X		X									13
Thymus																									+	14
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Fibroadenoma	X	X	X				X	X					X				X			X						16
Fibroadenoma, multiple																							X			1
Leukemia mononuclear																										1
Skin	+	M	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	46
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										16
NERVOUS SYSTEM																										
Brain																										17
RESPIRATORY SYSTEM																										
Lung	+		+	+		+	+	+	+	+	+	+	+		+				+			+				32
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, clitoral gland																										1
Leukemia mononuclear									X						X											10
Nose																										12
Trachea	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	47
SPECIAL SENSES SYSTEM																										
Eye																								+		3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											7
Urinary bladder																										14

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: HIGH DOSE

WEEKS ON STUDY	025	046	062	069	078	080	084	086	089	091	092	095	095	095	102	102	102	103	103	104	104	104	106	106	106
CARCASS ID	524	591	585	532	531	552	604	554	553	541	603	592	534	535	521	595	513	564	551	562	602	544	511	512	514
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous										X				X	X									X	
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X											X	X							X		
Neoplastic nodule																									
Neoplastic nodule, multiple																									
Mesentery					+					+											+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X		
Acinus, adenoma														X											
Acinus, adenoma, multiple																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X											X	X							X		
Pericardium, alveolar/bronchiolar carcinoma, metastatic																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X	X									
Medulla, pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	M	+	M	M	+	M	M	M	M	+	M	M	+	+	M	M	M	M	M	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X					X				X	X	X		X					
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																X									
Follicular cell, carcinoma															X										
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	–	–	–	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
Leukemia mononuclear															X								X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
Polyp stromal														X											

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	515	522	523	525	533	543	555	561	571	542	545	563	565	572	573	574	575	581	582	583	584	593	594	601	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma				X																X						2
Polyp adenomatous													X	X												6
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X														X	6
Neoplastic nodule																			X							1
Neoplastic nodule, multiple									X																	1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Acinus, adenoma					X																					2
Acinus, adenoma, multiple																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Pericardium, alveolar/bronchiolar carcinoma, metastatic											X															1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Medulla, pheochromocytoma benign				X				X																		3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	+	+	+	+	M	+	M	+	M	+	+	+	+	M	M	M	M	+	M	M	M	+	20
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X			X			X		X		X		X				X		X	X			X			16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																	X	X								2
Follicular cell, adenoma																							X			2
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	39
Adenoma										X								X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																X										1
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Polyp stromal																					X					2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	025	046	062	069	078	080	084	086	089	091	092	095	095	095	102	102	102	103	103	104	104	104	106	106	106
CARCASS ID	524	591	585	532	531	552	604	554	553	541	603	592	534	535	521	595	513	564	551	562	602	544	511	512	514
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, leukemia mononuclear															X										
Mediastinal, leukemia mononuclear															X								X		
Mesenteric, leukemia mononuclear															X								X		
Pancreatic, leukemia mononuclear															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X											X	X							X		
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear															X										
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Fibroadenoma					X						X												X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant									X																
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Leukemia mononuclear				X											X	X							X		
Nose	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+			+															+		+		
Harderian gland			+			+															+				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X	X							X		
Sarcoma		X																							
Pelvis, transitional epithelium, papilloma													X												
Renal tubule, adenoma																									
Urinary bladder	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X								X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	515	522	523	525	533	543	555	561	571	542	545	563	565	572	573	574	575	581	582	583	584	593	594	601	605	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymph node	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mandibular, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																										2
Mesenteric, leukemia mononuclear																										2
Pancreatic, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X														X	6
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	M	+	+	M	M	+	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	39
Fibroadenoma		X								X							X									6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Alveolar/bronchiolar carcinoma, multiple											X															1
Leukemia mononuclear																									X	5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										4
Harderian gland						+																				4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Sarcoma																										1
Pelvis, transitional epithelium, papilloma																										1
Renal tubule, adenoma															X											1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Leukemia mononuclear																										2

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	5.9%	0.0%	10.0%
Terminal Rates (c)	2/34 (6%)	0/28 (0%)	2/28 (7%)
Day of First Observation	735		721
Life Table Tests (d)	P=0.331	P=0.282N	P=0.422
Logistic Regression Tests (d)	P=0.359	P=0.282N	P=0.458
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test (d)		P=0.247N	P=0.500
Large Intestine: Adenomatous Polyp			
Overall Rates (a)	0/50 (0%)	(e) 1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	0.0%	3.6%	17.6%
Terminal Rates (c)	0/34 (0%)	1/28 (4%)	3/28 (11%)
Day of First Observation		735	637
Life Table Tests (d)	P=0.004	P=0.461	P=0.013
Logistic Regression Tests (d)	P=0.004	P=0.461	P=0.015
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.500	P=0.013
Large Intestine: Adenomatous Polyp or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	(e) 1/50 (2%)	8/50 (16%)
Adjusted Rates (b)	0.0%	3.6%	24.2%
Terminal Rates (c)	0/34 (0%)	1/28 (4%)	5/28 (18%)
Day of First Observation		735	637
Life Table Tests (d)	P<0.001	P=0.461	P=0.003
Logistic Regression Tests (d)	P<0.001	P=0.461	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P=0.003
Liver: Neoplastic Nodule			
Overall Rates (a)	0/50 (0%)	4/49 (8%)	2/50 (4%)
Adjusted Rates (b)	0.0%	13.8%	7.1%
Terminal Rates (c)	0/34 (0%)	3/28 (11%)	2/28 (7%)
Day of First Observation		722	735
Life Table Tests (d)	P=0.173	P=0.043	P=0.196
Logistic Regression Tests (d)	P=0.197	P=0.038	P=0.196
Cochran-Armitage Trend Test (d)	P=0.223		
Fisher Exact Test (d)		P=0.056	P=0.247
Mammary Gland: Fibroadenoma			
Overall Rates (a)	22/50 (44%)	17/50 (34%)	6/50 (12%)
Adjusted Rates (b)	50.9%	51.0%	18.2%
Terminal Rates (c)	14/34 (41%)	12/28 (43%)	4/28 (14%)
Day of First Observation	537	618	543
Life Table Tests (d)	P=0.004N	P=0.509N	P=0.004N
Logistic Regression Tests (d)	P<0.001N	P=0.369N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.206N	P<0.001N
Pancreas: Acinar Adenoma			
Overall Rates (a)	1/48 (2%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	3.0%	0.0%	9.7%
Terminal Rates (c)	1/33 (3%)	0/28 (0%)	2/28 (7%)
Day of First Observation	735		665
Life Table Tests (d)	P=0.151	P=0.533N	P=0.257
Logistic Regression Tests (d)	P=0.173	P=0.533N	P=0.293
Cochran-Armitage Trend Test (d)	P=0.185		
Fisher Exact Test (d)		P=0.495N	P=0.324

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pancreas: Acinar Adenoma or Carcinoma			
Overall Rates (a)	1/48 (2%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	3.0%	3.6%	9.7%
Terminal Rates (c)	1/33 (3%)	1/28 (4%)	2/28 (7%)
Day of First Observation	735	735	665
Life Table Tests (d)	P=0.169	P=0.725	P=0.257
Logistic Regression Tests (d)	P=0.196	P=0.725	P=0.293
Cochran-Armitage Trend Test (d)	P=0.212		
Fisher Exact Test (d)		P=0.747N	P=0.324
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	29/48 (60%)	12/46 (26%)	16/48 (33%)
Adjusted Rates (b)	66.6%	38.1%	46.9%
Terminal Rates (c)	19/33 (58%)	8/26 (31%)	10/27 (37%)
Day of First Observation	610	538	582
Life Table Tests (d)	P=0.043N	P=0.019N	P=0.067N
Logistic Regression Tests (d)	P=0.008N	P=0.003N	P=0.011N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P<0.001N	P=0.007N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	3/47 (6%)	2/49 (4%)
Adjusted Rates (b)	11.8%	8.3%	7.1%
Terminal Rates (c)	4/34 (12%)	1/27 (4%)	2/28 (7%)
Day of First Observation	735	577	735
Life Table Tests (d)	P=0.348N	P=0.613N	P=0.429N
Logistic Regression Tests (d)	P=0.292N	P=0.553N	P=0.429N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.535N	P=0.349N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/47 (6%)	2/49 (4%)
Adjusted Rates (b)	14.7%	8.3%	7.1%
Terminal Rates (c)	5/34 (15%)	1/27 (4%)	2/28 (7%)
Day of First Observation	735	577	735
Life Table Tests (d)	P=0.230N	P=0.479N	P=0.298N
Logistic Regression Tests (d)	P=0.185N	P=0.421N	P=0.298N
Cochran-Armitage Trend Test (d)	P=0.167N		
Fisher Exact Test (d)		P=0.393N	P=0.226N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	2/47 (4%)	3/49 (6%)
Adjusted Rates (b)	5.9%	7.4%	8.9%
Terminal Rates (c)	2/34 (6%)	2/27 (7%)	1/28 (4%)
Day of First Observation	735	735	713
Life Table Tests (d)	P=0.353	P=0.610	P=0.453
Logistic Regression Tests (d)	P=0.371	P=0.610	P=0.461
Cochran-Armitage Trend Test (d)	P=0.398		
Fisher Exact Test (d)		P=0.668	P=0.490
Uterus: Stromal Polyp			
Overall Rates (a)	10/49 (20%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (b)	26.4%	26.1%	6.2%
Terminal Rates (c)	7/34 (21%)	5/28 (18%)	1/28 (4%)
Day of First Observation	630	538	665
Life Table Tests (d)	P=0.040N	P=0.519	P=0.033N
Logistic Regression Tests (d)	P=0.018N	P=0.572N	P=0.019N
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.480N	P=0.013N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (*Continued*)

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	9/50 (18%)	(f) 13/50 (26%)	6/50 (12%)
Adjusted Rates (b)	22.8%	32.3%	17.5%
Terminal Rates (c)	5/34 (15%)	3/28 (11%)	3/28 (11%)
Day of First Observation	642	576	483
Life Table Tests (d)	P=0.386N	P=0.122	P=0.390N
Logistic Regression Tests (d)	P=0.257N	P=0.237	P=0.293N
Cochran-Armitage Trend Test (d)	P=0.261N		
Fisher Exact Test (d)		P=0.235	P=0.288N

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

TABLE B4a. HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
TOTAL	0/282
Overall Historical Incidence	
TOTAL	0/1,888

(a) Data as of April 29, 1987, for studies of at least 104 weeks

TABLE B4b. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Neoplastic Nodules in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	1/50
Diglycidyl resorcinol ether	2/50
1,2-Dichloropropane	1/50
Chlorodibromomethane	0/50
n-Butyl chloride	1/50
Bromodichloromethane	1/50
TOTAL	6/300 (2.0%)
SD (b)	1.26%
Range (c)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	33/1,945 (1.7%)
SD (b)	2.18%
Range (c)	
High	5/50
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks; no malignant tumors have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL POLYPS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	11/50
Diglycidyl resorcinol ether	12/50
1,2-Dichloropropane	10/50
Chlorodibromomethane	14/50
n-Butyl chloride	12/50
Bromodichloromethane	11/49
TOTAL	70/299 (23.4%)
SD (b)	2.69%
Range (c)	
High	14/50
Low	10/50
Overall Historical Incidence	
TOTAL	390/1,934 (20.2%)
SD (b)	6.53%
Range (c)	
High	17/50
Low	5/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4d. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	18/50	1/50	19/50
Diglycidyl resorcinol ether	16/50	2/50	17/50
1,2-Dichloropropane	16/49	3/49	19/49
Chlorodibromomethane	11/47	5/47	16/47
n-Butyl chloride	22/49	2/49	24/49
Bromodichloromethane	27/49	4/49	31/49
TOTAL	110/294 (37.4%)	17/294 (5.8%)	126/294 (42.9%)
SD (b)	11.13%	3.15%	11.41%
Range (c)			
High	27/49	5/47	31/49
Low	11/47	1/50	17/50
Overall Historical Incidence			
TOTAL	(d) 760/1,901 (40.0%)	(e) 53/1,901 (2.8%)	(d,e) 811/1,901 (42.7%)
SD (b)	10.34%	2.81%	10.43%
Range (c)			
High	32/49	5/47	33/49
Low	9/50	0/50	11/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 72 chromophobe adenomas
(e) Includes 4 chromophobe carcinomas and 10 adenocarcinomas, NOS

TABLE B4e. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Fibroadenomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	18/50
Diglycidyl resorcinol ether	17/50
1,2-Dichloropropane	15/50
Chlorodibromomethane	18/50
n-Butyl chloride	16/50
Bromodichloromethane	20/50
TOTAL	104/300 (34.7%)
SD (b)	3.50%
Range (c)	
High	20/50
Low	15/50
Overall Historical Incidence	
TOTAL	(d) 558/1,950 (28.6%)
SD (b)	9.09%
Range (c)	
High	26/50
Low	7/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes six adenomas, NOS, one papillary adenoma, five cystadenomas, and one papillary cystadenoma

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)	(18)	(49)
Parasite	5 (10%)	1 (6%)	7 (14%)
Cecum, inflammation, acute			1 (2%)
Colon, fibrosis	1 (2%)		
Colon, necrosis	1 (2%)	1 (6%)	
Intestine small	(48)	(16)	(49)
Lymphoid nodule, mineralization		1 (6%)	
Liver	(50)	(49)	(50)
Basophilic focus	28 (56%)	15 (31%)	13 (26%)
Clear cell focus			1 (2%)
Cyst		2 (4%)	
Eosinophilic focus		2 (4%)	2 (4%)
Fatty change, diffuse	8 (16%)	13 (27%)	20 (40%)
Fatty change, focal	11 (22%)	26 (53%)	26 (52%)
Hepatodiaphragmatic nodule	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, diffuse			1 (2%)
Hyperplasia, focal		1 (2%)	1 (2%)
Hyperplasia, multifocal	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active	9 (18%)	8 (16%)	27 (54%)
Mixed cell focus	8 (16%)	25 (51%)	28 (56%)
Necrosis	11 (22%)	3 (6%)	2 (4%)
Bile duct, hyperplasia	17 (34%)	10 (20%)	4 (8%)
Mesentery	(4)	(3)	(3)
Artery, necrosis, fibrinoid		1 (33%)	
Fat, inflammation, chronic active		1 (33%)	
Fat, necrosis	4 (100%)	2 (67%)	3 (100%)
Pancreas	(48)	(49)	(50)
Acinus, atrophy	12 (25%)	7 (14%)	3 (6%)
Acinus, hyperplasia	3 (6%)	2 (4%)	3 (6%)
Artery, inflammation, chronic active		1 (2%)	
Artery, necrosis, fibrinoid		2 (4%)	
Artery, pigmentation		1 (2%)	
Salivary glands	(49)	(49)	(50)
Inflammation, chronic active			3 (6%)
Acinus, hyperplasia			1 (2%)
Duct, ectasia		1 (2%)	8 (16%)
Duct, inflammation, chronic active		9 (18%)	15 (30%)
Duct, metaplasia, squamous		10 (20%)	16 (32%)
Stomach	(50)	(26)	(50)
Forestomach, acanthosis	6 (12%)	7 (27%)	4 (8%)
Forestomach, hyperkeratosis	7 (14%)	8 (31%)	4 (8%)
Forestomach, inflammation, chronic active	3 (6%)	3 (12%)	2 (4%)
Forestomach, ulcer	2 (4%)	4 (15%)	1 (2%)
Glandular, abscess		1 (4%)	
Glandular, hyperplasia, lymphoid			1 (2%)
Glandular, inflammation, chronic active		1 (4%)	1 (2%)
Glandular, necrosis		1 (4%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(16)	(50)
Cardiomyopathy	34 (68%)	12 (75%)	22 (44%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(18)	(50)
Necrosis	1 (2%)	2 (11%)	
Cortex, hyperplasia	1 (2%)		3 (6%)
Medulla, hyperplasia	4 (8%)	3 (17%)	7 (14%)
Islets, pancreatic	(48)	(49)	(50)
Ectopic tissue		1 (2%)	
Parathyroid gland	(21)	(16)	(20)
Hyperplasia		1 (6%)	
Pituitary gland	(48)	(46)	(48)
Pars distalis, angiectasis	27 (56%)	11 (24%)	9 (19%)
Pars distalis, cyst	6 (13%)	8 (17%)	2 (4%)
Pars distalis, hyperplasia	9 (19%)	15 (33%)	7 (15%)
Pars intermedia, cyst			1 (2%)
Pars intermedia, hyperplasia	2 (4%)		1 (2%)
Thyroid gland	(50)	(47)	(49)
Necrosis		1 (2%)	
C-cell, hyperplasia	9 (18%)	7 (15%)	3 (6%)
Follicular cell, cyst		1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(34)	(9)	(39)
Inflammation, chronic active	2 (6%)	1 (11%)	2 (5%)
Necrosis	2 (6%)		3 (8%)
Ovary	(50)	(20)	(50)
Cyst	5 (10%)	2 (10%)	3 (6%)
Inflammation, chronic active	2 (4%)		
Mineralization	1 (2%)		
Necrosis		1 (5%)	
Interstitium, hyperplasia	1 (2%)		
Uterus	(49)	(50)	(50)
Angiectasis	1 (2%)		
Decidual reaction		1 (2%)	
Hemorrhage	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		2 (4%)
Mineralization	1 (2%)		
Necrosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(47)	(49)
Lumbar, pigmentation		1 (2%)	
Mandibular, hematopoietic cell proliferation			1 (2%)
Mandibular, infiltration cellular, plasma cell		1 (2%)	3 (6%)
Mandibular, pigmentation			1 (2%)
Mediastinal, congestion			1 (2%)
Mediastinal, infiltration cellular, mast cell			1 (2%)
Mediastinal, pigmentation	2 (4%)	2 (4%)	6 (12%)
Mesenteric, depletion lymphoid		1 (2%)	2 (4%)
Mesenteric, infiltration cellular, mast cell			1 (2%)
Mesenteric, pigmentation			1 (2%)
Pancreatic, infiltration cellular, mast cell			1 (2%)
Pancreatic, infiltration cellular, plasma cell		2 (4%)	
Pancreatic, pigmentation			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(49)	(28)	(50)
Depletion lymphoid	1 (2%)	2 (7%)	2 (4%)
Hematopoietic cell proliferation	35 (71%)	17 (61%)	39 (78%)
Hemorrhage	1 (2%)		
Necrosis	1 (2%)	1 (4%)	
Pigmentation	7 (14%)	6 (21%)	29 (58%)
Thymus	(48)	(14)	(48)
Infiltration cellular, lymphocytic		1 (7%)	1 (2%)
Epithelial cell, hyperplasia	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	(42)	(39)
Galactocele	25 (57%)	4 (10%)	1 (3%)
Necrosis		1 (2%)	
Skin	(50)	(46)	(50)
Hyperkeratosis		1 (2%)	
Inflammation, chronic active			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(17)	(50)
Brain stem, hemorrhage	2 (4%)		
Cerebellum, hemorrhage	2 (4%)		1 (2%)
Cerebellum, inflammation, chronic active			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(32)	(50)
Infiltration cellular, histiocytic	11 (22%)	8 (25%)	16 (32%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic active	4 (8%)	4 (13%)	4 (8%)
Inflammation, granulomatous		1 (3%)	1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (3%)	
Bronchus, metaplasia, squamous			1 (2%)
Nose	(48)	(12)	(46)
Hemorrhage		1 (8%)	
Inflammation, chronic active		2 (17%)	2 (4%)
Metaplasia, squamous			1 (2%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)		1 (2%)
Trachea	(50)	(47)	(50)
Inflammation, acute			2 (4%)
Inflammation, chronic active			3 (6%)
SPECIAL SENSES SYSTEM			
Eye		(3)	(4)
Inflammation, acute			1 (25%)
Synechia			1 (25%)
Lens, cataract		2 (67%)	2 (50%)
Lens, inflammation, acute			1 (25%)
Lens, synechia		2 (67%)	
Harderian gland	(1)		(4)
Abscess			3 (75%)
Duct, metaplasia, squamous			1 (25%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst		1 (2%)	1 (2%)
Necrosis			2 (4%)
Nephropathy	40 (80%)	41 (82%)	46 (92%)
Transitional epithelium, hyperplasia		2 (4%)	1 (2%)
Transitional epithelium, metaplasia, osseous			1 (2%)
Transitional epithelium, mineralization			1 (2%)
Urinary bladder	(45)	(14)	(46)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)		1 (2%)
Mineralization		2 (14%)	
Necrosis	1 (2%)		
Transitional epithelium, hyperplasia		1 (7%)	

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(46)	*(50)	(30)
Lymphoma malignant lymphocytic			1 (3%)
Intestine small	(50)	*(50)	(46)
Hepatocholangiocarcinoma, metastatic	1 (2%)		
Polyp adenomatous	1 (2%)		
Liver	(50)	(50)	(49)
Hemangioma	1 (2%)	1 (2%)	
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, multiple	1 (2%)		2 (4%)
Hepatocellular carcinoma	5 (10%)	6 (12%)	6 (12%)
Hepatocellular carcinoma, multiple	2 (4%)	2 (4%)	
Hepatocellular adenoma	10 (20%)	9 (18%)	8 (16%)
Hepatocellular adenoma, multiple	1 (2%)	2 (4%)	
Hepatocholangiocarcinoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Osteosarcoma, metastatic		1 (2%)	
Pancreas	(49)	*(50)	(48)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Stomach	(50)	(50)	(49)
Forestomach, papilloma squamous		4 (8%)	
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland	(49)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)
Osteosarcoma, metastatic		1 (2%)	
Capsule, adenoma	1 (2%)	1 (2%)	1 (2%)
Medulla, pheochromocytoma benign	1 (2%)		
Thyroid gland	(48)	*(50)	(46)
Follicular cell, adenoma			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
None			
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(48)
Lymphoma malignant mixed	1 (2%)		
Lymph node	(47)	*(50)	(43)
Axillary, lymphoma malignant histiocytic	1 (2%)		
Axillary, lymphoma malignant undifferentiated cell type	1 (2%)		
Inguinal, lymphoma malignant histiocytic	1 (2%)		
Inguinal, lymphoma malignant mixed	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(47)	*(50)	(43)
Lumbar, lymphoma malignant histiocytic	1 (2%)		
Lumbar, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Mandibular, lymphoma malignant histiocytic	1 (2%)		
Mandibular, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)
Mediastinal, hepatocholangiocarcinoma, metastatic	1 (2%)		
Mediastinal, lymphoma malignant histiocytic	1 (2%)		
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant undifferentiated cell type	1 (2%)		
Mesenteric, lymphoma malignant histiocytic	1 (2%)		
Mesenteric, lymphoma malignant lymphocytic	1 (2%)		2 (5%)
Mesenteric, lymphoma malignant undifferentiated cell type	3 (6%)		1 (2%)
Pancreatic, lymphoma malignant lymphocytic			1 (2%)
Renal, lymphoma malignant lymphocytic			1 (2%)
Renal, lymphoma malignant mixed	1 (2%)		
Thoracic, lymphoma malignant histiocytic	1 (2%)		
Spleen	(50)	*(50)	(49)
Hemangioma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		2 (4%)
Lymphoma malignant mixed	1 (2%)		
Lymphoma malignant undifferentiated cell type	2 (4%)		1 (2%)
Thymus	(35)	*(50)	(30)
Lymphoma malignant lymphocytic			1 (3%)
Lymphoma malignant mixed	1 (3%)		
Lymphoma malignant undifferentiated cell type	1 (3%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(1)	*(50)	
Adenoma	1 (100%)		
Skin	(48)	*(50)	(49)
Subcutaneous tissue, fibroma	3 (6%)	5 (10%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	7 (14%)	4 (8%)
Subcutaneous tissue, hemangioma	1 (2%)		
Subcutaneous tissue, neurofibrosarcoma	1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	10 (20%)	5 (10%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Fibrosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma, metastatic	2 (4%)	3 (6%)	2 (4%)
Hepatocholangiocarcinoma, metastatic	1 (2%)		
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Osteosarcoma, metastatic		1 (2%)	
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	2 (4%)	1 (2%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	*(50)	(49)
Hepatocholangiocarcinoma, metastatic	1 (2%)		
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangioma	3 (6%)	1 (2%)	
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant undifferentiated cell	3 (6%)		1 (2%)
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant mixed	1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		2 (4%)
Lymphoma malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	7	10
Terminal sacrifice	41	37	36
Moribund sacrifice	5	6	4
TUMOR SUMMARY			
Total animals with primary neoplasms **	34	33	27
Total primary neoplasms	52	49	32
Total animals with benign neoplasms	25	24	13
Total benign neoplasms	33	28	15
Total animals with malignant neoplasms	17	20	15
Total malignant neoplasms	19	21	17
Total animals with secondary neoplasms ***	3	5	2
Total secondary neoplasms	6	7	2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: VEHICLE CONTROL

WEEKS ON STUDY	065	078	084	090	092	099	100	102	103	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106
CARCASS ID	011	083	035	102	023	021	072	054	055	014	033	043	051	061	082	091	092	095	103	012	044	065	075	101	013
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic																									
Polyp adenomatous															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma					X	X	X																		
Hepatocellular carcinoma, multiple								X															X		
Hepatocellular adenoma	X			X				X		X	X												X	X	
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																					X				
Mesentery							+																		
Pancreas	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Medulla, pheochromocytoma benign																									
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	M	+	+	+	M	+	M	M	+	+	M	+	+	M	M	M	M	+	M	M
Pituitary gland	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	–	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland												+								+	+			+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
: Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	015	022	031	032	034	024	025	041	042	045	052	053	062	063	064	071	073	074	081	084	085	093	094	104	105	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic																		X								1
Polyp adenomatous																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma													X													1
Hemangiosarcoma, multiple																			X							1
Hepatocellular carcinoma	X															X										5
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma				X		X		X																		10
Hepatocellular adenoma, multiple																									X	1
Hepatocholangiocarcinoma																		X								1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant mixed																										1
Mesentery							+																			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant undifferentiated cell type																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																						X				1
Medulla, pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	M	M	M	M	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	M	25
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial gland	+																			+					+	7
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	065	078	084	090	092	099	100	102	103	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106
CARCASS ID	011	083	035	102	023	021	072	054	055	014	033	043	051	061	082	091	092	095	103	012	044	065	075	101	113
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant histiocytic																									
Axillary, lymphoma malignant undifferentiated cell type																									
Inguinal, lymphoma malignant histiocytic																									
Inguinal, lymphoma malignant mixed																					X				
Lumbar, lymphoma malignant histiocytic																									
Lumbar, lymphoma malignant lymphocytic		X																							
Mandibular, lymphoma malignant histiocytic																									
Mandibular, lymphoma malignant mixed																					X				
Mandibular, lymphoma malignant undifferentiated cell type																									
Mediastinal, hepatocholangiocarcinoma, metastatic																									
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant lymphocytic		X																							
Mediastinal, lymphoma malignant undifferentiated cell type			X																						
Mesenteric, lymphoma malignant histiocytic																									
Mesenteric, lymphoma malignant lymphocytic		X																							
Mesenteric, lymphoma malignant undifferentiated cell type			X																						
Renal, lymphoma malignant mixed																					X				
Thoracic, lymphoma malignant histiocytic																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant mixed																					X				
Lymphoma malignant undifferentiated cell type			X																						
Thymus	M	+	+	M	M	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Lymphoma malignant undifferentiated cell type			X																						
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Subcutaneous tissue, fibroma														X											
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, hemangioma					X																				
Subcutaneous tissue, neurofibrosarcoma				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X					X	X			X			X		
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic						X		X																	
Hepatocholangiocarcinoma, metastatic																									
Lymphoma malignant mixed																					X				
Nose	–	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic																									
Lymphoma malignant mixed																					X				
Lymphoma malignant undifferentiated cell type																									
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	106	106	106	108	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	015	022	031	032	034	024	025	041	042	045	052	053	062	063	064	071	073	074	081	084	085	093	094	104	105	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Axillary, lymphoma malignant histiocytic			X																							1
Axillary, lymphoma malignant undifferentiated cell type																			X							1
Inguinal, lymphoma malignant histiocytic			X																							1
Inguinal, lymphoma malignant mixed																										1
Lumbar, lymphoma malig histiocytic			X																							1
Lumbar, lymphoma malig lymphocytic																										1
Mandibular, lymphoma malignant histiocytic			X																							1
Mandibular, lymphoma malig mixed																										1
Mandibular, lymphoma malignant undifferentiated cell type																			X							1
Mediastinal, hepatocholangiocarcinoma, metastatic																		X								1
Mediastinal, lymphoma malignant histiocytic			X																							1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Mesenteric, lymphoma malignant histiocytic			X																							1
Mesenteric, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant undifferentiated cell type																			X					X		3
Renal, lymphoma malignant mixed																										1
Thoracic, lymphoma malignant histiocytic			X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																			X							2
Thymus	+	M	M	+	M	M	+	M	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	35
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Adenoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibroma																	X	X								3
Subcutaneous tissue, fibrosarcoma																			X							2
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, neurofibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X										X						X		X				X	10
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic																										2
Hepatocholangiocarcinoma, metastatic																		X								1
Lymphoma malignant mixed																										1
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																+	+									2
Adenoma																X	X									2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic																		X								1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: LOW DOSE

WEEKS ON STUDY	024	057	073	076	086	090	094	096	096	097	097	099	099	105	115	105	105	105	105	105	105	105	105	105	105
CARCASS ID	16 2	18 4	15 1	13 4	12 1	12 3	12 2	20 1	20 2	13 1	16 3	20 3	17 4	11 1	11 2	11 3	11 4	11 5	12 4	12 5	13 2	13 3	13 5	14 1	14 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	M			+		+														
Gallbladder	+	+	A	+	+	+																			
Intestine large	+	+	+	+	+	+	+																		
Intestine small	+	+	A	+	+	+							+												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																	X								
Hepatocellular carcinoma					X	X									X							X	X		
Hepatocellular carcinoma, multiple											X														
Hepatocellular adenoma		X						X	X												X				
Hepatocellular adenoma, multiple																									
Osteosarcoma, metastatic				X																					
Mesentery									+																
Pancreas	+	+	+	+	+	+						+	+										+		
Salivary glands	+	+	+	+	+	+																			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous															X									X	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+																			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+		+	+	+			+								+							+	
Osteosarcoma, metastatic				X																					
Capsule, adenoma																	X								
Islets, pancreatic	+	+	+	+	+	+						+	+										+		
Parathyroid gland	+	M	M	+	+	+																			
Pituitary gland	+	+	+	+	+	+																			
Thyroid gland	+	+	+	+	+	+																			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	−	−	+	+	+	+	+						+												
Preputial gland		+											+		+			+							
Prostate	+	+	+	+	+	+																			
Seminal vesicle	+	+	+	+	+	+			+														+		
Testes	+	+	+	+	+	+	+						+												
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+																			
Lymph node	+	+	+	+	+	M			+		M	+					+		+						
Spleen	+	+	+	+	+	+	+			+	+	+	+				+	+		+					
Thymus	M	+	+	+	M	+						+	+												
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M																			
Skin	+	+	+	+	+	+				+		+	+		+				+		+				
Subcutaneous tissue, fibroma												X			X										
Subcutaneous tissue, fibrosarcoma										X		X	X												
Subcutaneous tissue, neurofibrosarcoma																									
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X											X							X		
Alveolar/bronchiolar carcinoma			X													X									
Alveolar/bronchiolar carcinoma, multiple																									
Fibrosarcoma, metastatic, skin										X															
Hepatocellular carcinoma, metastatic					X	X					X														
Osteosarcoma, metastatic				X																					
Nose	−	−	+	+	+	+																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland				+									+												
Adenoma				X																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+		+		+		+					+	+	+				+	
Urinary bladder	+	+	+	+	+	+	A		+																

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	TOTAL.
CARCASS ID	143	144	145	152	153	154	155	161	164	165	171	172	173	175	181	182	183	185	191	204	205	192	193	194	195	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus				+		+							+	+						+			+			13
Gallbladder													+													6
Intestine large																										7
Intestine small																										6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																X										1
Hemangiosarcoma																										1
Hepatocellular carcinoma																		X								6
Hepatocellular carcinoma, multiple																									X	2
Hepatocellular adenoma	X						X		X												X	X				9
Hepatocellular adenoma, multiple																X				X						2
Osteosarcoma, metastatic																										1
Mesentery																										1
Pancreas																										9
Salivary glands														+					+							8
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, papilloma squamous																X	X									4
CARDIOVASCULAR SYSTEM																										
Heart																										6
ENDOCRINE SYSTEM																										
Adrenal gland							+																			9
Osteosarcoma, metastatic																										1
Capsule, adenoma																										1
Islets, pancreatic																										9
Parathyroid gland																										4
Pituitary gland																			M							6
Thyroid gland																										6
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																				+						7
Preputial gland					+					+					+				+						+	9
Prostate																										6
Seminal vesicle					+																				+	10
Testes																				+						9
HEMATOPOIETIC SYSTEM																										
Blood													+													1
Bone marrow																										6
Lymph node							+			+		+		+								+	+			15
Spleen					+				+										+				+			18
Thymus																										6
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin						+			+	+		+	+		+		+	+		+	+	+				23
Subcutaneous tissue, fibroma										X			X					X								5
Subcutaneous tissue, fibrosarcoma									X	X								X					X			7
Subcutaneous tissue, neurofibrosarcoma						X																				1
Subcutaneous tissue, sarcoma												X														1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain																										6
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X						X								5
Alveolar/bronchiolar carcinoma																										2
Alveolar/bronchiolar carcinoma, multiple														X												1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic																										3
Osteosarcoma, metastatic																										1
Nose																										4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																										2
Adenoma																										1
URINARY SYSTEM																										
Kidney			+	+				+	+		+														+	20
Urinary bladder																										7

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: HIGH DOSE

WEEKS ON STUDY	063	069	073	076	076	081	082	089	091	091	093	095	095	097	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	29 1	29 2	29 3	27 3	29 5	30 5	22 5	23 3	30 4	30 1	28 4	26 1	26 2	26 5	26 3	21 1	22 2	22 4	23 1	24 1	25 3	27 2	28 1	28 2	30 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	M	M	+	M	M	M	M	M	+	M	A	M	+	+	+	+	+	+	+	+	M	M	+
Lymphoma malignant lymphocytic																				X					
Intestine large	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	M	+	+	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple												X			X										
Hepatocellular carcinoma			X				X						X	X											
Hepatocellular adenoma									X												X	X			
Lymphoma malignant lymphocytic						X														X					
Lymphoma malignant								X																	
Pancreas	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																				X					
Capsule, adenoma																									
Islets, pancreatic	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	M	M	+	M	M	+	+	M	M	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	M	+	+	M	+	M	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Thyroid gland	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	–	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+					+										+	+					+	+		
Prostate	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node	+	+	+	+	M	+	M	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+
Lumbar, lymphoma malignant lymphocytic						X																			
Mandibular, lymphoma malignant undifferentiated cell type																									
Mediastinal, lymphoma malignant lymphocytic																				X					
Mesenteric, lymphoma malignant lymphocytic						X														X					
Mesenteric, lymphoma malignant undifferentiated cell type																									
Pancreatic, lymphoma malignant lymphocytic																				X					
Renal, lymphoma malignant lymphocytic																				X					
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X														X					
Lymphoma malignant undifferentiated cell type																									
Thymus	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	+	M	+	M	+	+	+	M
Lymphoma malignant lymphocytic																				X					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma				X							X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic							X						X												
Lymphoma malignant histiocytic								X																	
Lymphoma malignant lymphocytic						X																			
Nose	–	–	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+																								
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Urinary bladder	+	+	+	+	+	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	212	213	214	215	221	223	232	234	235	242	243	244	245	251	252	254	255	264	271	274	275	283	285	294	303	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	+	+	30
Lymphoma malignant lymphocytic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, multiple																										2
Hepatocellular carcinoma				X																		X				6
Hepatocellular adenoma							X				X						X						X		X	8
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+																							1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Capsule, adenoma						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	M	M	M	M	M	M	M	M	M	26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Follicular cell, adenoma								X																		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial gland	+	+	+																		+					10
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lumbar, lymphoma malig lymphocytic																										1
Mandibular, lymphoma malignant undifferentiated cell type																						X				1
Mediastinal, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant lymphocytic																										2
Mesenteric, lymphoma malignant undifferentiated cell type																						X				1
Pancreatic, lymphoma malignant lymphocytic																										1
Renal, lymphoma malig lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										2
Lymphoma malignant undifferentiated cell type																						X				1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	30
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma																							X			2
Subcutaneous tissue, fibrosarcoma																			X						X	4
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma													X										X			2
Hepatocellular carcinoma, metastatic																										2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland												+								+						3
Adenoma												X														1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	11/50 (22%)	11/50 (22%)	8/49 (16%)
Adjusted Rates (b)	24.6%	26.8%	21.4%
Terminal Rates (c)	8/41 (20%)	8/37 (22%)	7/36 (19%)
Day of First Observation	455	393	632
Life Table Tests (d)	P=0.383N	P=0.500	P=0.419N
Logistic Regression Tests (d)	P=0.283N	P=0.561N	P=0.333N
Cochran-Armitage Trend Test (d)	P=0.282N		
Fisher Exact Test (d)		P=0.595N	P=0.323N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	7/50 (14%)	8/50 (16%)	6/49 (12%)
Adjusted Rates (b)	15.4%	19.3%	14.4%
Terminal Rates (c)	3/41 (7%)	5/37 (14%)	2/36 (6%)
Day of First Observation	642	602	509
Life Table Tests (d)	P=0.552N	P=0.421	P=0.603N
Logistic Regression Tests (d)	P=0.423N	P=0.507	P=0.425N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.500	P=0.516N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	19/50 (38%)	14/49 (29%)
Adjusted Rates (b)	33.8%	43.5%	33.6%
Terminal Rates (c)	10/41 (24%)	13/37 (35%)	9/36 (25%)
Day of First Observation	455	393	509
Life Table Tests (d)	P=0.527	P=0.247	P=0.575N
Logistic Regression Tests (d)	P=0.370N	P=0.375	P=0.376N
Cochran-Armitage Trend Test (d)	P=0.401N		
Fisher Exact Test (d)		P=0.338	P=0.440N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	10/50 (20%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	24.4%	12.7%	5.6%
Terminal Rates (c)	10/41 (24%)	4/37 (11%)	2/36 (6%)
Day of First Observation	730	602	730
Life Table Tests (d)	P=0.016N	P=0.178N	P=0.026N
Logistic Regression Tests (d)	P=0.016N	P=0.161N	P=0.026N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.131N	P=0.015N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	2.4%	7.4%	0.0%
Terminal Rates (c)	1/41 (2%)	2/37 (5%)	0/36 (0%)
Day of First Observation	730	507	
Life Table Tests (d)	P=0.412N	P=0.278	P=0.526N
Logistic Regression Tests (d)	P=0.361N	P=0.334	P=0.526N
Cochran-Armitage Trend Test (d)	P=0.384N		
Fisher Exact Test (d)		P=0.309	P=0.505N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	7/50 (14%)	2/49 (4%)
Adjusted Rates (b)	26.8%	17.2%	5.6%
Terminal Rates (c)	11/41 (27%)	5/37 (14%)	2/36 (6%)
Day of First Observation	730	507	730
Life Table Tests (d)	P=0.012N	P=0.288N	P=0.015N
Logistic Regression Tests (d)	P=0.009N	P=0.236N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.007N		
Fisher Exact Test (d)		P=0.218N	P=0.008N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	7.3%	13.1%	5.6%
Terminal Rates (c)	3/41 (7%)	4/37 (11%)	2/36 (6%)
Day of First Observation	730	688	730
Life Table Tests (d)	P=0.495N	P=0.300	P=0.559N
Logistic Regression Tests (d)	P=0.499N	P=0.309	P=0.559N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.357	P=0.500N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	4.8%	17.4%	9.9%
Terminal Rates (c)	1/41 (2%)	4/37 (11%)	2/36 (6%)
Day of First Observation	721	673	526
Life Table Tests (d)	P=0.233	P=0.063	P=0.289
Logistic Regression Tests (d)	P=0.297	P=0.071	P=0.382
Cochran-Armitage Trend Test (d)	P=0.297		
Fisher Exact Test (d)		P=0.080	P=0.339
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	11.9%	22.5%	15.2%
Terminal Rates (c)	4/41 (10%)	6/37 (16%)	4/36 (11%)
Day of First Observation	721	673	526
Life Table Tests (d)	P=0.342	P=0.146	P=0.416
Logistic Regression Tests (d)	P=0.406	P=0.161	P=0.490
Cochran-Armitage Trend Test (d)	P=0.442		
Fisher Exact Test (d)		P=0.194	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	4.8%	19.9%	9.9%
Terminal Rates (c)	1/41 (2%)	5/37 (14%)	2/36 (6%)
Day of First Observation	721	673	526
Life Table Tests (d)	P=0.236	P=0.036	P=0.289
Logistic Regression Tests (d)	P=0.298	P=0.040	P=0.382
Cochran-Armitage Trend Test (d)	P=0.303		
Fisher Exact Test (d)		P=0.046	P=0.339
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	10/50 (20%)	6/50 (12%)
Adjusted Rates (b)	11.9%	25.0%	15.2%
Terminal Rates (c)	4/41 (10%)	7/37 (19%)	4/36 (11%)
Day of First Observation	721	673	526
Life Table Tests (d)	P=0.341	P=0.095	P=0.416
Logistic Regression Tests (d)	P=0.402	P=0.104	P=0.490
Cochran-Armitage Trend Test (d)	P=0.443		
Fisher Exact Test (d)		P=0.131	P=0.500
Forestomach: Squamous Papilloma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	0.0%	10.8%	0.0%
Terminal Rates (c)	0/41 (0%)	4/37 (11%)	0/36 (0%)
Day of First Observation		730	
Life Table Tests (d)	P=0.579	P=0.051	(e)
Logistic Regression Tests (d)	P=0.579	P=0.051	(e)
Cochran-Armitage Trend Test (d)	P=0.616		
Fisher Exact Test (d)		P=0.059	(e)

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
All Sites: Hemangioma			
Overall Rates (a)	3/50 (6%)	(f) 1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	6.8%	2.7%	0.0%
Terminal Rates (c)	1/41 (2%)	1/37 (3%)	0/36 (0%)
Day of First Observation	642	730	
Life Table Tests (d)	P=0.079N	P=0.344N	P=0.152N
Logistic Regression Tests (d)	P=0.062N	P=0.306N	P=0.111N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
All Sites: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	(f) 2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	9.1%	5.4%	5.3%
Terminal Rates (c)	2/41 (5%)	2/37 (5%)	1/36 (3%)
Day of First Observation	642	730	663
Life Table Tests (d)	P=0.311N	P=0.386N	P=0.406N
Logistic Regression Tests (d)	P=0.269N	P=0.352N	P=0.337N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.339N	P=0.339N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/50 (12%)	(f) 0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	13.4%	0.0%	9.8%
Terminal Rates (c)	4/41 (10%)	0/37 (0%)	2/36 (6%)
Day of First Observation	544		565
Life Table Tests (d)	P=0.331N	P=0.025N	P=0.444N
Logistic Regression Tests (d)	P=0.235N	P=0.012N	P=0.271N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.013N	P=0.370N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.
(f) Eighteen spleens were examined microscopically.

TABLE C4. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	6/50	0/50	6/50
1,2-Dichloropropane	9/50	3/50	11/50
Chlorodibromomethane	5/50	6/50	11/50
n-Butyl chloride	12/50	2/50	14/50
Bromodichloromethane	8/49	4/49	12/49
Bis(2-chloro-1-methylethyl)ether	5/50	1/50	6/50
n-Butyl chloride	3/50	3/50	6/50
TOTAL	48/349 (13.8%)	19/349 (5.4%)	66/349 (18.9%)
SD (b)	6.07%	3.97%	6.78%
Range (c)			
High	12/50	6/50	14/50
Low	3/50	0/50	6/50
Overall Historical Incidence			
TOTAL	223/1,985 (11.2%)	112/1,985 (5.6%)	325/1,985 (16.4%)
SD (b)	5.73%	3.83%	6.44%
Range (c)			
High	13/47	6/50	15/47
Low	1/50	0/50	2/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(46)	(6)	(30)
Inflammation, chronic active	2 (4%)		1 (3%)
Intestine large	(50)	(7)	(48)
Circumanal gland, inflammation, acute		1 (14%)	
Lymphoid nodule, hyperplasia	2 (4%)	1 (14%)	5 (10%)
Intestine small	(50)	(6)	(46)
Hyperplasia, lymphoid	1 (2%)		
Duodenum, fibrosis		1 (17%)	
Duodenum, hyperplasia		1 (17%)	
Duodenum, inflammation, chronic active		1 (17%)	
Duodenum, necrosis		1 (17%)	
Ileum, epithelium, hyperplasia	1 (2%)		
Lymphoid nodule, hyperplasia	26 (52%)		21 (46%)
Lymphoid nodule, necrosis			1 (2%)
Liver	(50)	(50)	(49)
Basophilic focus	2 (4%)	2 (4%)	
Cyst		1 (2%)	
Fatty change, diffuse		1 (2%)	
Fatty change, focal	7 (14%)	5 (10%)	7 (14%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation	20 (40%)	5 (10%)	14 (29%)
Hemorrhage		1 (2%)	1 (2%)
Infarct	1 (2%)		
Mineralization	3 (6%)	3 (6%)	3 (6%)
Necrosis	10 (20%)	8 (16%)	12 (24%)
Pigmentation	1 (2%)		
Regeneration		1 (2%)	
Thrombus		1 (2%)	
Bile duct, hyperplasia			1 (2%)
Mesentery	(2)	(1)	
Abscess		1 (100%)	
Fat, necrosis	1 (50%)		
Pancreas	(49)	(9)	(48)
Acinus, atrophy	1 (2%)		1 (2%)
Acinus, hyperplasia	2 (4%)		1 (2%)
Stomach	(50)	(50)	(49)
Hyperplasia, glandular	1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)		
Forestomach, acanthosis	4 (8%)	3 (6%)	6 (12%)
Forestomach, cyst epithelial inclusion, multiple			1 (2%)
Forestomach, fibrosis	1 (2%)	1 (2%)	
Forestomach, hyperkeratosis	5 (10%)	5 (10%)	7 (14%)
Forestomach, inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)
Forestomach, mineralization		1 (2%)	
Forestomach, ulcer	2 (4%)	2 (4%)	2 (4%)
Glandular, cyst			1 (2%)
Glandular, dysplasia			1 (2%)
Glandular, hyperplasia		4 (8%)	6 (12%)
Glandular, inflammation, chronic active	4 (8%)	6 (12%)	8 (16%)
Glandular, mineralization	1 (2%)		
Tooth			(1)
Developmental malformation			1 (100%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(6)	(48)
Cardiomyopathy	2 (4%)		
Mineralization	1 (2%)		
Artery, inflammation, chronic active			1 (2%)
Pericardium, inflammation, acute		1 (17%)	
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(9)	(49)
Capsule, hyperplasia	31 (63%)	6 (67%)	30 (61%)
Cortex, hyperplasia	1 (2%)		2 (4%)
Cortex, hypertrophy		1 (11%)	2 (4%)
Cortex, hypertrophy, diffuse			1 (2%)
Cortex, hypertrophy, focal	1 (2%)		
Medulla, hyperplasia	8 (16%)	1 (11%)	4 (8%)
Islets, pancreatic	(49)	(9)	(48)
Hyperplasia	1 (2%)		
Pituitary gland	(45)	(6)	(40)
Pars distalis, cyst	2 (4%)	1 (17%)	1 (3%)
Pars distalis, hyperplasia	3 (7%)		
Pars intermedia, cyst	1 (2%)		
Thyroid gland	(48)	(6)	(46)
Follicle, cyst	1 (2%)		
Follicular cell, hyperplasia, focal	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(47)	(7)	(47)
Abscess		1 (14%)	
Preputial gland	(7)	(9)	(10)
Cyst		3 (33%)	
Dilatation	1 (14%)		
Inflammation, chronic active	5 (71%)	2 (22%)	5 (50%)
Necrosis	1 (14%)	3 (33%)	5 (50%)
Prostate	(46)	(6)	(45)
Hemorrhage		1 (17%)	
Inflammation, chronic active	1 (2%)	1 (17%)	2 (4%)
Necrosis		1 (17%)	
Seminal vesicle	(49)	(10)	(48)
Inflammation, chronic active	1 (2%)	1 (10%)	
Testes	(50)	(9)	(48)
Spermatocele		1 (11%)	
Seminiferous tubule, atrophy	7 (14%)	1 (11%)	6 (13%)
Seminiferous tubule, mineralization	1 (2%)	1 (11%)	3 (6%)
HEMATOPOIETIC SYSTEM			
Lymph node	(47)	(15)	(43)
Lumbar, angiectasis			1 (2%)
Lumbar, hematopoietic cell proliferation			1 (2%)
Lumbar, hyperplasia, plasma cell	1 (2%)	1 (7%)	
Mandibular, infiltration cellular, plasma cell			1 (2%)
Mesenteric, angiectasis	22 (47%)	10 (67%)	14 (33%)
Mesenteric, hematopoietic cell proliferation	15 (32%)	10 (67%)	10 (23%)
Mesenteric, necrosis	1 (2%)		
Pancreatic, hematopoietic cell proliferation		1 (7%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(47)	(15)	(43)
Renal, necrosis	1 (2%)		
Thoracic, angiectasis	1 (2%)		
Thoracic, necrosis	1 (2%)		
Spleen	(50)	(18)	(49)
Angiectasis	2 (4%)	1 (6%)	
Atrophy	1 (2%)		1 (2%)
Hematopoietic cell proliferation	40 (80%)	15 (83%)	38 (78%)
Hyperplasia, lymphoid	3 (6%)		1 (2%)
Hyperplasia, mast cell		1 (6%)	
Thymus	(35)	(6)	(30)
Atrophy	3 (9%)	2 (33%)	
Hyperplasia, lymphoid			1 (3%)
INTEGUMENTARY SYSTEM			
Skin	(48)	(23)	(49)
Bacterium	1 (2%)	3 (13%)	2 (4%)
Hemorrhage		1 (4%)	1 (2%)
Hyperplasia, basal cell		1 (4%)	
Inflammation, acute		1 (4%)	
Inflammation, chronic active		2 (9%)	
Necrosis	4 (8%)	8 (35%)	8 (16%)
Prepuce, acanthosis			1 (2%)
Prepuce, inflammation, chronic active		1 (4%)	1 (2%)
Prepuce, necrosis			2 (4%)
Sebaceous gland, hyperplasia		1 (4%)	
Subcutaneous tissue, fibrosis		3 (13%)	2 (4%)
Subcutaneous tissue, inflammation, chronic active		1 (4%)	
Subcutaneous tissue, metaplasia, osseous	1 (2%)		
Subcutaneous tissue, necrosis	1 (2%)	1 (4%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(49)	(49)
Joint, tarsal, hyperostosis	35 (70%)	40 (82%)	27 (55%)
NERVOUS SYSTEM			
Brain	(50)	(6)	(48)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
Mineralization			1 (2%)
Thalamus, mineralization	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(49)
Abscess			1 (2%)
Embolus tumor	1 (2%)		
Fungus			1 (2%)
Hemorrhage	7 (14%)	4 (8%)	7 (14%)
Infiltration cellular, histiocytic	2 (4%)	2 (4%)	
Inflammation, chronic active		2 (4%)	1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)	1 (2%)
Bronchiole, inflammation, acute		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Harderian gland	(2)	(2)	(3)
Abscess			1 (33%)
Fibrosis			1 (33%)
Fungus			1 (33%)
Inflammation, chronic active			1 (33%)
URINARY SYSTEM			
Kidney	(50)	(20)	(49)
Abscess			1 (2%)
Cyst	4 (8%)	1 (5%)	
Embolus tumor	1 (2%)		
Inflammation, chronic active	3 (6%)	4 (20%)	2 (4%)
Cortex, mineralization	19 (38%)	2 (10%)	10 (20%)
Papilla, mineralization	1 (2%)		1 (2%)
Papilla, necrosis			1 (2%)
Renal tubule, casts	5 (10%)	1 (5%)	4 (8%)
Renal tubule, degeneration	1 (2%)		1 (2%)
Renal tubule, regeneration	18 (36%)	4 (20%)	8 (16%)
Urinary bladder	(48)	(7)	(47)
Angiectasis		1 (14%)	
Calculus micro observation only	2 (4%)		
Inflammation, acute		1 (14%)	
Inflammation, chronic		1 (14%)	
Inflammation, chronic active	1 (2%)	1 (14%)	
Transitional epithelium, hyperplasia	1 (2%)		

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	49	50	50
ALIMENTARY SYSTEM			
Gallbladder	(38)	*(50)	(37)
Lymphoma malignant lymphocytic	1 (3%)		
Intestine large	(48)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small	(47)	*(50)	(48)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed		1 (2%)	
Lymphoid nodule, lymphoma malignant mixed	1 (2%)		
Lymphoid nodule, lymphoma malignant undifferentiated cell type	1 (2%)		
Liver	(49)	(50)	(50)
Hemangiosarcoma			2 (4%)
Hepatocellular carcinoma	1 (2%)		2 (4%)
Hepatocellular adenoma	1 (2%)	5 (10%)	3 (6%)
Hepatocellular adenoma, multiple	2 (4%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma, multiple	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)		2 (4%)
Lymphoma malignant undifferentiated cell type		2 (4%)	
Mesentery	*(49)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
Pancreas	(46)	*(50)	(47)
Lymphoma malignant lymphocytic	3 (7%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)		
Lymphoma malignant undifferentiated cell type		1 (2%)	
Salivary glands	(46)	*(50)	(45)
Lymphoma malignant undifferentiated cell type		1 (2%)	
Stomach	(47)	(48)	(50)
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant undifferentiated cell type		1 (2%)	
Forestomach, papilloma squamous			2 (4%)
CARDIOVASCULAR SYSTEM			
Heart	(48)	*(50)	(50)
Lymphoma malignant undifferentiated cell type		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland	(49)	*(50)	(46)
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant undifferentiated cell type		1 (2%)	
Islets, pancreatic	(46)	*(50)	(47)
Adenoma		1 (2%)	
Pituitary gland	(44)	*(50)	(46)
Lymphoma malignant lymphocytic	2 (5%)		
Pars distalis, adenoma	7 (16%)	6 (12%)	5 (11%)
Pars distalis, adenoma, multiple			1 (2%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(49)	(49)	(47)
Lymphoma malignant lymphocytic	2 (4%)		
Follicular cell, adenoma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(45)	*(50)	(49)
Lymphoma malignant lymphocytic	3 (7%)		
Uterus	(49)	*(50)	(49)
Histiocytic sarcoma		1 (2%)	
Leiomyosarcoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Polyp stromal	1 (2%)	1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	*(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant mixed			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Lymph node	(44)	*(50)	(45)
Axillary, lymphoma malignant lymphocytic	2 (5%)		
Iliac, lymphoma malignant mixed	1 (2%)		
Inguinal, lymphoma malignant lymphocytic	1 (2%)		
Inguinal, lymphoma malignant mixed	1 (2%)		
Lumbar, lymphoma malignant histiocytic			1 (2%)
Lumbar, lymphoma malignant lymphocytic	2 (5%)		
Lumbar, lymphoma malignant mixed	1 (2%)	1 (2%)	1 (2%)
Lumbar, lymphoma malignant undifferentiated cell type	1 (2%)		
Mandibular, lymphoma malignant lymphocytic	3 (7%)		
Mandibular, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant undifferentiated cell type	1 (2%)		
Mediastinal, lymphoma malignant histiocytic	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant lymphocytic	4 (9%)	1 (2%)	
Mediastinal, lymphoma malignant mixed	1 (2%)		2 (4%)
Mediastinal, lymphoma malignant undifferentiated cell type	1 (2%)		
Mesenteric, lymphoma malignant histiocytic			1 (2%)
Mesenteric, lymphoma malignant lymphocytic	3 (7%)	1 (2%)	
Mesenteric, lymphoma malignant mixed	1 (2%)		2 (4%)
Mesenteric, lymphoma malignant undifferentiated cell type	1 (2%)	2 (4%)	
Pancreatic, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Pancreatic, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant histiocytic			1 (2%)
Renal, lymphoma malignant lymphocytic	2 (5%)		
Renal, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Spleen	(48)	*(50)	(50)
Hemangiosarcoma			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	3 (6%)		
Lymphoma malignant mixed	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant undifferentiated cell type	3 (6%)	2 (4%)	
Thymus	(37)	*(50)	(35)
Lymphoma malignant histiocytic			1 (3%)
Lymphoma malignant lymphocytic	3 (8%)	1 (2%)	
Lymphoma malignant mixed	1 (3%)		1 (3%)
Lymphoma malignant undifferentiated cell type	2 (5%)	1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin	(40)	*(50)	(44)
Lymphoma malignant undifferentiated cell type		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(49)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(49)	*(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Osteosarcoma, metastatic			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	*(49)	*(50)	*(50)
Adenoma		1 (2%)	
URINARY SYSTEM			
Kidney	(49)	*(50)	(50)
Lymphoma malignant lymphocytic	3 (6%)		
Lymphoma malignant mixed	1 (2%)		1 (2%)
Lymphoma malignant undifferentiated cell type		2 (4%)	
Osteosarcoma, metastatic			1 (2%)
Urinary bladder	(47)	*(50)	(48)
Lymphoma malignant lymphocytic	4 (9%)		
Lymphoma malignant undifferentiated cell type		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(49)	*(50)	*(50)
Lymphoma malignant lymphocytic	4 (8%)	1 (2%)	
Lymphoma malignant undifferentiated cell	3 (6%)	2 (4%)	
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	3 (6%)	2 (4%)	2 (4%)
Hemangiosarcoma			3 (6%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund sacrifice	10	12	11
Terminal sacrifice	25	13	20
Culled	1		
Natural death	14	25	19

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	24	18	18
Total primary neoplasms	30	23	25
Total animals with benign neoplasms	11	13	15
Total benign neoplasms	15	16	17
Total animals with malignant neoplasms	15	6	8
Total malignant neoplasms	15	7	8
Total animals with secondary neoplasms ***			1
Total secondary neoplasms			2

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: VEHICLE CONTROL

WEEKS ON STUDY	013	072	081	084	084	086	086	086	087	088	089	090	092	092	093	098	098	099	100	100	100	101	103	104	104
CARCASS ID	313	331	323	361	374	325	382	393	351	352	395	391	341	402	375	342	365	381	321	333	405	411	363	355	372
ALIMENTARY SYSTEM																									
Esophagus		M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder		A	A	M	+	+	+	+	A	+	+	+	+	A	+	M	M	+	+	+	+	+	+	+	M
Lymphoma malignant lymphocytic								X																	
Intestine large		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Intestine small		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Lymphoma malignant lymphocytic		X																							
Lymphoid nodule, lymphoma malignant mixed																									
Lymphoid nodule, lymphoma malignant undifferentiated cell type																									
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																		X							
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma, multiple																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant mixed														X											
Mesentery				+	+	+			+	+	+	+			+	+	+				+		+		+	+
Lymphoma malignant lymphocytic																									
Pancreas		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant mixed														X											
Salivary glands		+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Stomach		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Lymphoma malignant lymphocytic		X																							
CARDIOVASCULAR SYSTEM																									
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Islets, pancreatic		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Parathyroid gland		M	M	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Pars distalis, adenoma							X														X			X	
Pars intermedia, adenoma																		X							
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland			M	+	M	M				M															
Ovary		+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Oviduct																							+		
Uterus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Polyp stromal																		X							

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	312	315	324	334	444	455	362	364	371	373	383	384	392	401	414	422	432	435	433	535	543	548	585	594	403	404	TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+		38
Lymphoma malignant lymphocytic																											1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																											1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																											1
Lymphoid nodule, lymphoma malignant mixed																				X							1
Lymphoid nodule, lymphoma malignant undifferentiated cell type																		X									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																											1
Hepatocellular adenoma																										X	1
Hepatocellular adenoma, multiple																			X					X			2
Hepatocholangiocarcinoma, multiple																								X			1
Lymphoma malignant histiocytic					X																						1
Lymphoma malignant lymphocytic											X						X										4
Lymphoma malignant mixed																											1
Mesentery											+															+	16
Lymphoma malignant lymphocytic											X																1
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																	X										3
Lymphoma malignant mixed																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic											X																2
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																											2
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	M	M	+	M	+	+	+	+	M	M	+	+	M	+	+	+	M	+	+	M	+	+	M	+			32
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+			44
Lymphoma malignant lymphocytic																	X										2
Pars distalis, adenoma	X						X									X										X	7
Pars intermedia, adenoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																											2
Follicular cell, adenoma	X																										1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Clitoral gland																											1
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Lymphoma malignant lymphocytic																	X										3
Oviduct																											1
Uterus	+	+	+	+	+	+	#	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma												X															1
Lymphoma malignant histiocytic					X																						1
Lymphoma malignant lymphocytic																	X										1
Polyp stromal																											1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	013	072	081	084	084	086	086	086	087	088	089	090	092	092	093	098	098	099	100	100	100	101	103	104	104
CARCASS ID	313	331	323	361	374	325	382	393	351	525	395	391	341	402	375	342	365	381	321	333	405	311	363	355	372
HEMATOPOIETIC SYSTEM																									
Blood																						+			
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
Lymphoma malignant undifferentiated cell type													X												
Lymph node		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Axillary, lymphoma malignant lymphocytic								X																	
Iliac, **lymphoma** malignant mixed														X											
Inguinal, lymphoma malignant lymphocytic								X																	
Inguinal, lymphoma malignant mixed														X											
Lumbar, lymphoma malignant lymphocytic								X																	
Lumbar, lymphoma malignant mixed														X											
Lumbar, lymphoma malignant undifferentiated cell type													X												
Mandibular, lymphoma malignant lymphocytic		X						X																	
Mandibular, lymphoma malignant mixed														X											
Mandibular, lymphoma malignant undifferentiated cell type													X												
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant lymphocytic		X						X																	
Mediastinal, lymphoma malignant mixed														X											
Mediastinal, lymphoma malignant **undifferentiated cell type**													X												
Mesenteric, lymphoma malignant lymphocytic		X						X																	
Mesenteric, lymphoma malignant mixed														X											
Mesenteric, lymphoma malignant **undifferentiated cell type**																									
Pancreatic, lymphoma malignant lymphocytic								X																	
Pancreatic, lymphoma malignant mixed														X											
Renal, lymphoma malignant lymphocytic								X																	
Renal, lymphoma malignant mixed														X											
Renal, lymphoma malignant undifferentiated cell type													X												
Spleen		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant mixed														X											
Lymphoma malignant undifferentiated cell type													X												
Thymus		+	M	+	+	M	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant mixed														X											
Lymphoma malignant undifferentiated cell type													X												
INTEGUMENTARY SYSTEM																									
Mammary gland		+	M	+	M	M	+	+	M	M	+	+	+	M	M	M	+	+	+	+	M	+	M	M	M
Skin		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X																							
RESPIRATORY SYSTEM																									
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant undifferentiated cell type																									
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	
Lymphoma malignant mixed														X											
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic		X						X																	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	312	315	324	334	444	455	622	644	711	733	833	844	922	401	414	422	332	435	433	535	544	855	944	403	404	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																	X									2
Lymphoma malignant undifferentiated cell type																										1
Lymph node	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	44
Axillary, lymphoma malignant lymphocytic																	X									2
Iliac, lymphoma malignant mixed																										1
Inguinal, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant mixed																										1
Lumbar, lymphoma malig. lymphocytic																	X									2
Lumbar, lymphoma malignant mixed																										1
Lumbar, lymphoma malignant undifferentiated cell type																										1
Mandibular, lymphoma malignant lymphocytic																	X									3
Mandibular, lymphoma malig mixed																										1
Mandibular, lymphoma malignant undifferentiated cell type																										1
Mediastinal, lymphoma malignant histiocytic					X																					1
Mediastinal, lymphoma malignant lymphocytic											X						X									4
Mediastinal, lymphoma malig. mixed																										1
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Mesenteric, lymphoma malignant lymphocytic																	X									3
Mesenteric, lymphoma malig mixed																										1
Mesenteric, lymphoma malignant undifferentiated cell type																		X								1
Pancreatic, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malig. lymphocytic																	X									2
Renal, lymphoma malignant mixed																										1
Renal, lymphoma malignant undifferentiated cell type																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																	X									3
Lymphoma malignant mixed													X													2
Lymphoma malignant undifferentiated cell type						X												X								3
Thymus	+	M	+	+	+	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	37
Lymphoma malignant lymphocytic																	X									3
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type						X																				2
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	M	M	M	M	M	M	M	+	M	M	+	M	M	+	M	M	+	M	M	M	M	M	17
Skin	M	+	+	M	M	+	+	M	+	M	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	40
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma														X		X										2
Alveolar/bronchiolar carcinoma															X											1
Lymphoma malignant histiocytic					X																					1
Lymphoma malignant lymphocytic																	X									3
Lymphoma malignant undifferentiated cell type						X																				1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
None																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																	X									3
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Lymphoma malignant lymphocytic											X						X									4

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: LOW DOSE

WEEKS ON STUDY	07 70	07 71	07 71	07 75	07 75	07 77	07 78	07 78	07 78	07 79	08 00	08 81	08 81	08 81	08 82	08 83	08 84	08 85	08 85	08 86	08 86	08 88	09 90	09 91
CARCASS ID	49 92	41 33	44 41	50 55	46 61	41 12	48 83	49 94	50 02	48 81	47 72	49 91	47 75	41 15	47 33	42 23	42 24	45 33	43 34	49 55	45 44	47 74	47 71	43 33	43 35
ALIMENTARY SYSTEM																									
Esophagus	M	+	M	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Gallbladder	A	+	M	+	+	+	A	M	A	+	M	+	+	A	+	A	+	+	+	+	+	+	M	+	A
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	M	+	A	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A
Lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X							X									X		
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant undifferentiated cell type																						X			
Mesentery		+	+		+	+	+	+			+	+	+	+	+	+	+	+	+	+			+		
Pancreas	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant undifferentiated cell type																						X			
Salivary glands	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
Stomach	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
Islets, pancreatic	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	M	+	M	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+
Pituitary gland	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma																								X	
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																						+			
GENITAL SYSTEM																									
Clitoral gland																			+						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	093	094	095	096	097	097	097	099	101	103	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL
CARCASS ID	411	421	442	465	431	501	463	504	455	503	451	414	422	425	432	443	444	445	452	462	464	482	484	485	493	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus		+		+	+	+		+		+	+	+	+	+	+	+	+	+	+			+	+			36
Gallbladder																		+								16
Intestine large																										24
Intestine small			+	+	+																					22
Lymphoma malignant mixed					X																					1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X					X																		5
Hepatocellular adenoma, multiple					X																					1
Histiocytic sarcoma							X																			1
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant undifferentiated cell type									X																	2
Mesentery		+																								19
Pancreas		+		+		+				+																26
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant undifferentiated cell type																										1
Salivary glands								+																		24
Lymphoma malignant undifferentiated cell type																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant undifferentiated cell type																										1
CARDIOVASCULAR SYSTEM																										
Heart				+																						26
Lymphoma malignant undifferentiated cell type																										1
ENDOCRINE SYSTEM																										
Adrenal gland			+			+				+																26
Lymphoma malignant undifferentiated cell type																										1
Islets, pancreatic		+		+		+				M																25
Adenoma																										1
Parathyroid gland	+			+		+		+					+	+	+	+		+		+	+	+	+	+	+	32
Pituitary gland								+		+	+						+		+		+		+			27
Pars distalis, adenoma								X		X							X				X		X			6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Clitoral gland												+														2
Ovary	+	+	+			+		+		+	+		+	+				+				+				36
Uterus	+		+	+		+	+						+		+	+		+	+	+	+	+	+			39
Histiocytic sarcoma							X																			1
Polyp stromal																							X			1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	07 70	07 71	07 71	07 71	07 75	07 75	07 77	07 78	07 78	07 78	07 79	08 80	08 81	08 81	08 81	08 82	08 83	08 84	08 85	08 85	08 86	08 86	08 88	09 90	09 91
CARCASS ID	49 92	41 13	44 11	50 55	46 61	41 12	48 83	49 94	50 02	48 11	47 72	49 91	47 55	41 15	47 33	42 33	42 44	45 53	43 34	49 95	45 54	47 74	47 71	43 33	43 35
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant lymphocytic																									
Mesenteric, lymphoma malignant lymphocytic																									
Mesenteric, lymphoma malignant undifferentiated cell type																						X			
Pancreatic, lymphoma malignant lymphocytic																									
Renal, lymphoma malignant undifferentiated cell type																						X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																						X			
Thymus	+	M	M	M	+	M	M	+	M	+	M	+	M	M	M	+	+	+	+	+	+	+	M	+	M
Lymphoma malignant lymphocytic																									
Lymphoma malignant undifferentiated cell type																						X			
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	+	+	M	M	+	M	M	+	M	M	M	M	+	M	+	+	+	+	M	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Lymphoma malignant lymphocytic																									
Lymphoma malignant undifferentiated cell type																						X			
Nose	M	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			
Urinary bladder	M	M	+	+	A	M	M	M	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																						X			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	093	094	095	096	097	097	099	101	103	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	411	421	442	465	431	501	463	504	455	503	451	414	422	425	432	443	444	445	452	462	464	482	484	485	493	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										25
Lymph node		+	+	+	+	+		+	+	+										+						32
Lumbar, lymphoma malignant mixed					X																					1
Mediastinal, lymphoma malignant lymphocytic				X																						1
Mesenteric, lymphoma malignant lymphocytic				X																						1
Mesenteric, lymphoma malignant undifferentiated cell type									X																	2
Pancreatic, lymphoma malignant lymphocytic				X																						1
Renal, lymphoma malignant undifferentiated cell type																										1
Spleen		+	+			+			+	+		+	M	+					+	+					+	35
Lymphoma malignant mixed																									X	1
Lymphoma malignant undifferentiated cell type									X																	2
Thymus				+																						14
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant undifferentiated cell type																										1
INTEGUMENTARY SYSTEM																										
Mammary gland																										11
Skin																										25
Lymphoma malignant undifferentiated cell type																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										25
NERVOUS SYSTEM																										
Brain																										25
RESPIRATORY SYSTEM																										
Lung				+	+																					27
Alveolar/bronchiolar adenoma																										1
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant undifferentiated cell type																										1
Nose																										16
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland															+	+										2
Adenoma															X											1
URINARY SYSTEM																										
Kidney		+		+		+	+		+	+														+		32
Lymphoma malignant undifferentiated cell type									X																	2
Urinary bladder																										17
Lymphoma malignant undifferentiated cell type																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE: HIGH DOSE

WEEKS ON STUDY	044	052	054	063	064	068	077	077	078	080	080	081	081	081	081	083	084	087	087	088	089	091	092	093	094
CARCASS ID	581	553	562	572	551	512	522	571	523	511	593	534	575	514	603	561	604	531	515	582	564	584	525	513	595
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Gallbladder	+	+	A	A	+	A	M	+	M	+	+	+	M	+	A	A	M	+	+	A	+	+	+	M	+
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Hepatocellular carcinoma																						X			
Hepatocellular adenoma														X										X	
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
Mesentery				+		+		+	+	+	+	+			+		+	+	+	+	+		+		+
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, papilloma squamous																			X						
Tooth											+														
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	M	+	+	+	+	M	M	+	M	+	M	+	+	M	M	M	M	+	+	+	M
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland															M										M
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal								X																	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant histiocytic																									
Lumbar, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant histiocytic																									
Mesenteric, lymphoma malignant mixed																									
Renal, lymphoma malignant histiocytic																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
Thymus	M	+	+	+	+	M	+	+	M	M	+	+	M	+	+	M	+	+	+	+	M	M	+	M	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Osteosarcoma, metastatic	X																								
Nose	M	–	M	M	–	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Osteosarcoma, metastatic	X																								
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	0 9 6	0 9 6	0 9 6	0 9 8	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TOTAL:
CARCASS ID	5 8 3	5 9 4	5 6 3	5 3 2	5 7 4	5 2 1	5 2 4	5 3 3	5 3 5	5 4 1	5 4 2	5 4 3	5 8 5	5 9 2	6 0 1	5 4 4	5 4 5	5 5 2	5 5 4	5 5 5	5 6 5	5 7 3	5 9 1	6 0 2	6 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Gallbladder	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																	2
Hepatocellular carcinoma									X																2
Hepatocellular adenoma																						X			3
Hepatocellular adenoma, multiple												X													1
Lymphoma malignant histiocytic			X																						1
Lymphoma malignant mixed																				X		X			2
Mesentery	+			+	+																				19
Pancreas	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Forestomach, papilloma squamous																	X								2
Tooth																									1
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	M	M	+	M	M	M	+	M	27
Pituitary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X			X		X														X		X	5
Pars distalis, adenoma, multiple							X																		1
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland					M							M			M	M		+	M	M				M	M	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Uterus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal					X				X																	3
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																						X				1
Lymph node	M	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lumbar, lymphoma malig. histiocytic			X																							1
Lumbar, lymphoma malignant mixed																				X						1
Mediastinal, lymphoma malignant histiocytic			X																							1
Mediastinal, lymphoma malig. mixed																				X		X				2
Mesenteric, lymphoma malignant histiocytic			X																							1
Mesenteric, lymphoma malignant mixed																				X		X				2
Renal, lymphoma malignant histiocytic			X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma							X																			1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant mixed																				X		X				2
Thymus	M	M	+	M	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant mixed																						X				1
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	+	M	M	+	M	M	M	+	+	+	M	M	M	+	M	M	M	+	M	+	13
Skin	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	44
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			2
Osteosarcoma, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	43
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																						X				1
Osteosarcoma, metastatic																										1
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/49 (6%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	12.0%	21.1%	15.7%
Terminal Rates (c)	3/25 (12%)	0/15 (0%)	2/20 (10%)
Day of First Observation	735	538	566
Life Table Tests (d)	P=0.278	P=0.092	P=0.376
Logistic Regression Tests (d)	P=0.398	P=0.248	P=0.391
Cochran-Armitage Trend Test (d)	P=0.442		
Fisher Exact Test (d)		P=0.254	P=0.511
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	14.7%	21.1%	23.1%
Terminal Rates (c)	3/25 (12%)	0/15 (0%)	3/20 (15%)
Day of First Observation	692	538	566
Life Table Tests (d)	P=0.175	P=0.149	P=0.226
Logistic Regression Tests (d)	P=0.265	P=0.369	P=0.258
Cochran-Armitage Trend Test (d)	P=0.326		
Fisher Exact Test (d)		P=0.383	P=0.383
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	(e) 1/27 (4%)	2/50 (4%)
Adjusted Rates (b)	12.0%		7.4%
Terminal Rates (c)	3/25 (12%)		1/20 (5%)
Day of First Observation	735		560
Life Table Test (d)			P=0.598N
Logistic Regression Test (d)			P=0.595N
Fisher Exact Test (d)			P=0.490N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	7/44 (16%)	(e) 6/27 (22%)	6/46 (13%)
Adjusted Rates (b)	25.5%		28.3%
Terminal Rates (c)	4/22 (18%)		5/20 (25%)
Day of First Observation	600		672
Life Table Test (d)			P=0.605
Logistic Regression Test (d)			P=0.579
Fisher Exact Test (d)			P=0.465N
Uterus: Stromal Polyp			
Overall Rates (a)	1/49 (2%)	(e,f) 1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	3.0%	6.7%	11.8%
Terminal Rates (c)	0/25 (0%)	1/15 (7%)	1/19 (5%)
Day of First Observation	692	735	537
Life Table Tests (d)	P=0.146	P=0.625	P=0.220
Logistic Regression Tests (d)	P=0.153	P=0.670	P=0.275
Cochran-Armitage Trend Test (d)	P=0.201		
Fisher Exact Test (d)		P=0.747N	P=0.309
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	0/49 (0%)	(g) 0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	11.9%
Terminal Rates (c)	0/25 (0%)	0/15 (0%)	2/20 (10%)
Day of First Observation			372
Life Table Tests (d)	P=0.033	(h)	P=0.096
Logistic Regression Tests (d)	P=0.043	(h)	P=0.163
Cochran-Armitage Trend Test (d)	P=0.038		
Fisher Exact Test (d)		(h)	P=0.125

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	11/49 (22%)	(g) 5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	34.7%	22.9%	13.9%
Terminal Rates (c)	7/25 (28%)	1/15 (7%)	2/20 (10%)
Day of First Observation	502	601	672
Life Table Tests (d)	P=0.056N	P=0.349N	P=0.066N
Logistic Regression Tests (d)	P=0.028N	P=0.137N	P=0.039N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.079N	P=0.018N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) Thirty-nine uteruses were examined microscopically.
(g) Thirty-five spleens were examined microscopically.
(h) No P values are reported because no tumors were observed in the 100 mg/kg and vehicle control groups.

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	49	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)	(24)	(49)
Lymphoid nodule, hyperplasia	1 (2%)		2 (4%)
Intestine small	(47)	(22)	(48)
Fibrosis	1 (2%)		
Inflammation, acute	1 (2%)		
Mineralization		1 (5%)	
Necrosis	1 (2%)	1 (5%)	
Epithelium, hyperplasia		1 (5%)	
Lymphoid nodule, hyperplasia	16 (34%)	5 (23%)	15 (31%)
Liver	(49)	(50)	(50)
Abscess	1 (2%)		
Basophilic focus	1 (2%)	1 (2%)	
Clear cell focus			1 (2%)
Fatty change, diffuse		2 (4%)	4 (8%)
Fatty change, focal	1 (2%)	7 (14%)	20 (40%)
Hematopoietic cell proliferation	32 (65%)	34 (68%)	36 (72%)
Infarct	1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)
Mineralization	1 (2%)		
Necrosis	5 (10%)	4 (8%)	8 (16%)
Pigmentation		3 (6%)	2 (4%)
Mesentery	(16)	(19)	(19)
Inflammation, acute	14 (88%)	19 (100%)	19 (100%)
Fat, necrosis	1 (6%)		
Pancreas	(46)	(26)	(47)
Necrosis, coagulative	1 (2%)		
Acinus, hyperplasia, focal			1 (2%)
Stomach	(47)	(48)	(50)
Forestomach, acanthosis	2 (4%)	3 (6%)	2 (4%)
Forestomach, angiectasis	1 (2%)		
Forestomach, hyperkeratosis	6 (13%)	13 (27%)	6 (12%)
Forestomach, inflammation, chronic active	4 (9%)	2 (4%)	1 (2%)
Glandular, ectopic tissue			1 (2%)
Glandular, hyperplasia	1 (2%)	4 (8%)	4 (8%)
Glandular, inflammation, chronic active	5 (11%)	5 (10%)	3 (6%)
Glandular, mineralization			1 (2%)
Glandular, necrosis	1 (2%)	3 (6%)	1 (2%)
Glandular, pigmentation		1 (2%)	
Tooth			(1)
Inflammation, chronic active			1 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(48)	(26)	(50)
Cardiomyopathy	1 (2%)	2 (8%)	2 (4%)
Mineralization		1 (4%)	1 (2%)
Artery, inflammation, chronic active			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(26)	(46)
Accessory adrenal cortical nodule	1 (2%)		
Hematopoietic cell proliferation	9 (18%)	8 (31%)	8 (17%)
Capsule, hyperplasia	38 (78%)	17 (65%)	38 (83%)
Medulla, hyperplasia	1 (2%)		1 (2%)
Pituitary gland	(44)	(27)	(46)
Pars distalis, angiectasis	4 (9%)	5 (19%)	2 (4%)
Pars distalis, cyst			1 (2%)
Pars distalis, hyperplasia	16 (36%)	7 (26%)	13 (28%)
Pars distalis, pigmentation		1 (4%)	
Pars intermedia, hyperplasia		1 (4%)	1 (2%)
Thyroid gland	(49)	(49)	(47)
Follicular cell, cyst	1 (2%)		
Follicular cell, hyperplasia, focal	4 (8%)	3 (6%)	17 (36%)
Follicular cell, hyperplasia, multifocal	1 (2%)	1 (2%)	2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(45)	(36)	(49)
Abscess	13 (29%)	16 (44%)	19 (39%)
Angiectasis			1 (2%)
Cyst	11 (24%)	5 (14%)	4 (8%)
Degeneration, cystic		1 (3%)	
Hemorrhage	1 (2%)		
Mineralization	1 (2%)	2 (6%)	
Pigmentation		1 (3%)	1 (2%)
Bilateral, abscess	10 (22%)	15 (42%)	7 (14%)
Oviduct	(1)		
Inflammation, acute	1 (100%)		
Uterus	(49)	(39)	(49)
Abscess	2 (4%)	1 (3%)	2 (4%)
Angiectasis	1 (2%)	1 (3%)	
Hemorrhage			1 (2%)
Inflammation, acute	14 (29%)	12 (31%)	12 (24%)
Necrosis	1 (2%)		
Endometrium, hyperplasia	20 (41%)	19 (49%)	22 (45%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(25)	(50)
Myelofibrosis	3 (6%)		
Lymph node	(44)	(32)	(45)
Axillary, hyperplasia, plasma cell		1 (3%)	
Inguinal, hematopoietic cell proliferation	1 (2%)		
Inguinal, hyperplasia, plasma cell	1 (2%)		
Lumbar, angiectasis			1 (2%)
Lumbar, hematopoietic cell proliferation		2 (6%)	1 (2%)
Lumbar, hyperplasia, lymphoid	1 (2%)		
Lumbar, hyperplasia, plasma cell		4 (13%)	3 (7%)
Lumbar, infiltration cellular, plasma cell	1 (2%)		
Lumbar, necrosis	1 (2%)	1 (3%)	
Mandibular, angiectasis			1 (2%)
Mandibular, hematopoietic cell proliferation	1 (2%)	7 (22%)	5 (11%)
Mandibular, inflammation, acute	1 (2%)		
Mediastinal, angiectasis	1 (2%)		
Mediastinal, bacterium	1 (2%)		
Mediastinal, hematopoietic cell proliferation	8 (18%)	4 (13%)	7 (16%)
Mediastinal, hemorrhage			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(44)	(32)	(45)
Mediastinal, hyperplasia, plasma cell	3 (7%)	4 (13%)	10 (22%)
Mediastinal, infiltration cellular, plasma cell	4 (9%)		
Mediastinal, inflammation, acute	3 (7%)		
Mediastinal, necrosis	4 (9%)	3 (9%)	5 (11%)
Mesenteric, angiectasis	7 (16%)	3 (9%)	5 (11%)
Mesenteric, hematopoietic cell proliferation	16 (36%)	9 (28%)	11 (24%)
Mesenteric, hemorrhage	1 (2%)	1 (3%)	
Mesenteric, hyperplasia, lymphoid	1 (2%)		
Mesenteric, hyperplasia, plasma cell	2 (5%)	2 (6%)	2 (4%)
Mesenteric, infiltration cellular, plasma cell	1 (2%)		
Pancreatic, hematopoietic cell proliferation		2 (6%)	
Renal, angiectasis	1 (2%)		
Renal, hematopoietic cell proliferation	3 (7%)	4 (13%)	3 (7%)
Renal, hyperplasia, lymphoid	1 (2%)		
Renal, hyperplasia, plasma cell	2 (5%)	6 (19%)	3 (7%)
Renal, infiltration cellular, plasma cell	2 (5%)		
Renal, necrosis		1 (3%)	1 (2%)
Spleen	(48)	(35)	(50)
Angiectasis	1 (2%)		
Hematopoietic cell proliferation	43 (90%)	32 (91%)	48 (96%)
Hemorrhage		1 (3%)	
Hyperplasia, lymphoid	4 (8%)		5 (10%)
Necrosis	2 (4%)		
Pigmentation	1 (2%)		
Capsule, fibrosis			1 (2%)
Thymus	(37)	(14)	(35)
Atrophy	1 (3%)	1 (7%)	2 (6%)
Cyst		1 (7%)	
Hyperplasia, lymphoid			1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(17)	(11)	(13)
Galactocele	2 (12%)		
Skin	(40)	(25)	(44)
Hyperkeratosis	1 (3%)		
Necrosis			1 (2%)
Subcutaneous tissue, inflammation, chronic active	1 (3%)		1 (2%)
Subcutaneous tissue, metaplasia, osseous	1 (3%)		
Subcutaneous tissue, necrosis		1 (4%)	
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(25)	(50)
Joint, hyperostosis	1 (2%)		
NERVOUS SYSTEM			
Brain	(49)	(25)	(50)
Inflammation, acute		1 (4%)	
Thalamus, mineralization	2 (4%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIBROMOMETHANE (Continued)

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(49)	(27)	(50)
Abscess			1 (2%)
Bacterium	2 (4%)	4 (15%)	5 (10%)
Edema		1 (4%)	1 (2%)
Hemorrhage			6 (12%)
Inflammation, acute	4 (8%)		
Inflammation, chronic active	4 (8%)	4 (15%)	4 (8%)
Alveolar epithelium, hyperplasia	1 (2%)		3 (6%)
Pleura, inflammation, acute	4 (8%)	11 (41%)	9 (18%)
SPECIAL SENSES SYSTEM			
Harderian gland		(2)	
Hyperplasia		1 (50%)	
URINARY SYSTEM			
Kidney	(49)	(32)	(50)
Cyst			1 (2%)
Glomerulosclerosis			1 (2%)
Inflammation, acute	1 (2%)	3 (9%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (3%)	
Inflammation, chronic active	7 (14%)	4 (13%)	11 (22%)
Metaplasia, osseous	1 (2%)		
Necrosis		1 (3%)	
Pigmentation			1 (2%)
Cortex, mineralization	1 (2%)	1 (3%)	2 (4%)
Glomerulus, inflammation, acute	5 (10%)	6 (19%)	5 (10%)
Papilla, mineralization	5 (10%)		3 (6%)
Papilla, necrosis	1 (2%)	2 (6%)	1 (2%)
Renal tubule, casts			1 (2%)
Renal tubule, regeneration			2 (4%)

APPENDIX E

GENETIC TOXICOLOGY OF TRIBROMOMETHANE

TABLE E1. MUTAGENICITY OF TRIBROMOMETHANE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
Study performed at Case Western Reserve University							
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	103 ± 4.3	111 ± 4.9	122 ± 3.2	122 ± 7.8	140 ± 11.5	126 ± 7.6
	10	--	100 ± 14.7	--	137 ± 6.9	--	133 ± 11.3
	33	133 ± 15.6	114 ± 14.7	145 ± 16.6	150 ± 10.7	157 ± 9.5	135 ± 7.4
	100	119 ± 12.1	96 ± 21.9	162 ± 6.7	148 ± 13.7	182 ± 4.5	170 ± 12.9
	333	114 ± 13.0	99 ± 13.3	148 ± 4.4	139 ± 5.9	162 ± 10.9	155 ± 10.0
	1,000	99 ± 10.3	89 ± 9.7	95 ± 2.4	56 ± 28.7	139 ± 12.9	113 ± 7.3
	3,333	110 ± 11.1	--	0 ± 0.0	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	324 ± 35.4	265 ± 15.2	3,187 ± 74.2	2,762 ± 72.8	2,153 ± 184.9	2,079 ± 73.7
TA1535	0	5 ± 1.5	4 ± 0.6	6 ± 1.2	3 ± 1.5	5 ± 1.7	4 ± 1.0
	10	--	2 ± 0.7	--	3 ± 0.9	--	4 ± 1.5
	33	3 ± 0.7	2 ± 0.3	5 ± 1.5	2 ± 0.3	4 ± 0.6	3 ± 0.3
	100	2 ± 0.7	2 ± 0.0	5 ± 0.9	3 ± 0.3	8 ± 1.8	5 ± 0.7
	333	2 ± 1.2	2 ± 0.3	6 ± 1.0	2 ± 1.0	7 ± 1.2	7 ± 1.2
	1,000	6 ± 0.9	4 ± 1.0	6 ± 1.5	2 ± 0.7	9 ± 2.0	7 ± 1.5
	3,333	7 ± 0.9	--	3 ± 0.3	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	150 ± 21.1	51 ± 4.4	127 ± 7.8	30 ± 9.4	97 ± 17.1	29 ± 8.0
TA1537	0	3 ± 0.9	3 ± 0.6	5 ± 0.7	5 ± 1.5	6 ± 0.7	5 ± 0.3
	10	--	2 ± 0.9	--	4 ± 1.2	--	6 ± 1.2
	33	3 ± 0.6	3 ± 0.3	4 ± 0.3	5 ± 1.2	10 ± 2.2	8 ± 0.3
	100	5 ± 0.6	3 ± 1.2	6 ± 0.7	5 ± 1.2	7 ± 0.6	5 ± 0.7
	333	2 ± 0.3	3 ± 1.0	7 ± 1.0	5 ± 0.9	3 ± 0.7	4 ± 0.7
	1,000	1 ± 0.0	1 ± 0.3	5 ± 1.8	5 ± 0.3	6 ± 0.6	2 ± 1.5
	3,333	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	981 ± 130.9	129 ± 29.1	103 ± 40.1	156 ± 20.8	174 ± 17.1	220 ± 9.0
TA98	0	13 ± 2.0	11 ± 1.0	20 ± 1.7	19 ± 0.7	19 ± 1.5	19 ± 0.9
	10	--	10 ± 2.9	--	20 ± 0.9	--	20 ± 2.6
	33	12 ± 2.0	11 ± 2.1	34 ± 2.3	24 ± 4.6	24 ± 1.2	21 ± 1.5
	100	9 ± 1.0	10 ± 2.5	18 ± 3.4	28 ± 5.6	26 ± 3.2	20 ± 4.1
	333	12 ± 0.9	9 ± 1.3	23 ± 1.5	16 ± 3.5	26 ± 1.7	23 ± 3.0
	1,000	14 ± 1.7	12 ± 2.0	17 ± 2.5	19 ± 2.7	23 ± 1.5	21 ± 3.4
	3,333	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	201 ± 14.3	120 ± 11.2	2,530 ± 157.8	2,006 ± 59.5	1,346 ± 101.3	1,258 ± 107.3

TABLE E1. MUTAGENICITY OF TRIBROMOMETHANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Study performed at EG&G Mason Research Institute

Strain	Dose (µg/plate)	−S9 Trial 1	−S9 Trial 2	−S9 Trial 3	−S9 Trial 4
TA100	0	115 ± 5.9	80 ± 2.0	115 ± 3.8	147 ± 8.4
	10	108 ± 6.4	75 ± 2.3	--	--
	33	115 ± 10.5	81 ± 4.3	--	--
	100	117 ± 10.7	82 ± 1.5	110 ± 5.0	--
	300	--	--	129 ± 8.7	151 ± 4.4
	333	126 ± 13.2	113 ± 5.5	--	--
	400	--	--	--	167 ± 6.2
	450	--	--	--	152 ± 2.9
	500	--	--	--	171 ± 3.3
	550	--	--	--	160 ± 3.8
	600	--	--	(d) 136 ± 2.0	(d) 167 ± 7.2
	650	--	--	--	(d) 171 ± 6.3
	666	157 ± 3.0	158 ± 10.5	--	--
	700	--	--	--	(d) 99 ± 44.9
	750	--	--	Toxic	--
	900	--	--	Toxic	--
	1,000	--	Toxic	--	--
Trial summary		Equivocal	Weakly positive	Negative	Negative
Positive control (c)		1,460 ± 28.2	1,613 ± 98.1	1,526 ± 7.7	2,812 ± 107.6

Strain	Dose (µg/plate)	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	93 ± 6.7	110 ± 12.3	109 ± 6.8	110 ± 6.8
	10	97 ± 4.9	122 ± 2.6	116 ± 4.7	78 ± 4.4
	33	98 ± 11.6	100 ± 7.0	107 ± 8.2	79 ± 6.4
	100	109 ± 4.3	82 ± 4.6	103 ± 2.6	79 ± 5.5
	333	105 ± 7.0	120 ± 7.1	105 ± 9.2	82 ± 2.6
	666	94 ± 6.1	128 ± 3.5	107 ± 4.9	81 ± 4.3
	1,000	--	(d) 79 ± 6.4	--	(d) 62 ± 11.4
Trial summary		Negative	Negative	Negative	Negative
Positive control (c)		1,332 ± 33.3	1,880 ± 127.3	1,087 ± 25.1	1,061 ± 162.9

Strain	Dose (µg/plate)	−S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA1535	0	22 ± 4.2	17 ± 4.2	12 ± 3.4	11 ± 2.2	9 ± 1.9	8 ± 0.0
	10	21 ± 2.0	15 ± 3.3	11 ± 3.0	11 ± 0.0	10 ± 1.2	9 ± 1.2
	33	25 ± 1.9	14 ± 2.2	6 ± 0.3	8 ± 1.5	12 ± 1.5	13 ± 0.3
	100	22 ± 1.5	16 ± 2.9	12 ± 0.7	12 ± 0.6	11 ± 3.5	9 ± 3.5
	333	22 ± 1.2	17 ± 0.7	11 ± 1.2	10 ± 3.2	10 ± 3.5	9 ± 1.7
	666	25 ± 3.3	22 ± 1.5	11 ± 1.0	15 ± 3.5	12 ± 1.5	13 ± 2.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,101 ± 37.5	1,087 ± 22.0	122 ± 7.1	165 ± 9.4	62 ± 4.7	54 ± 4.1

TABLE E1. MUTAGENICITY OF TRIBROMOMETHANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
Study performed at EG&G Mason Research Institute (Continued)							
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA1537	0	7 ± 3.2	8 ± 2.1	9 ± 1.5	7 ± 0.7	10 ± 1.9	10 ± 2.2
	10	8 ± 1.7	4 ± 0.9	9 ± 0.9	11 ± 2.6	9 ± 1.9	9 ± 1.7
	33	7 ± 1.8	9 ± 3.5	9 ± 3.4	6 ± 3.0	10 ± 3.0	6 ± 0.9
	100	5 ± 1.2	7 ± 0.7	10 ± 1.5	8 ± 1.9	8 ± 1.3	9 ± 0.3
	333	7 ± 1.2	7 ± 1.7	10 ± 1.5	10 ± 3.2	12 ± 0.7	8 ± 1.7
	666	8 ± 2.7	7 ± 1.0	10 ± 0.0	11 ± 1.5	12 ± 3.2	10 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		460 ± 23.3	385 ± 93.8	149 ± 15.2	250 ± 23.7	78 ± 4.0	174 ± 10.4

		−S9			
		Trial 1	Trial 2	Trial 3	Trial 4
TA98	0	20 ± 1.2	15 ± 1.0	31 ± 2.7	23 ± 2.9
	10	21 ± 2.3	17 ± 1.8	--	--
	33	20 ± 1.2	20 ± 1.2	--	--
	100	20 ± 2.3	17 ± 2.6	29 ± 2.6	--
	300	--	--	33 ± 4.3	24 ± 2.0
	333	23 ± 3.2	24 ± 5.0	--	--
	400	--	--	--	25 ± 2.8
	450	--	--	--	23 ± 2.1
	500	--	--	--	32 ± 1.3
	550	--	--	--	27 ± 3.4
	600	--	--	38 ± 6.9	25 ± 4.4
	650	--	--	--	(d) 21 ± 1.0
	666	26 ± 1.9	(d) 20 ± 2.3	--	--
	700	--	--	--	(d) 11 ± 4.8
	750	--	--	(d) 8 ± 0.9	--
	900	--	--	(d) 7 ± 0.7	--
Trial summary		Negative	Negative	Negative	Negative
Positive control (c)		1,925 ± 37.3	1,610 ± 25.0	1,926 ± 41.2	1,986 ± 52.0

		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	32 ± 1.5	28 ± 0.9	34 ± 2.9	25 ± 3.3
	10	29 ± 1.3	24 ± 1.9	36 ± 0.6	30 ± 3.2
	33	34 ± 1.2	29 ± 4.4	36 ± 0.7	25 ± 2.6
	100	32 ± 5.7	33 ± 1.5	34 ± 4.2	27 ± 2.6
	333	36 ± 2.6	32 ± 1.2	31 ± 1.8	19 ± 2.6
	666	39 ± 2.6	27 ± 2.7	29 ± 4.9	32 ± 5.2
Trial summary		Negative	Negative	Negative	Negative
Positive control (c)		1,878 ± 18.9	2,291 ± 63.1	1,256 ± 16.3	1,555 ± 34.7

TABLE E1. MUTAGENICITY OF TRIBROMOMETHANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
Study performed at SRI International							
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	10%	30%	10%	30%
TA100	0	114 ± 7.3	100 ± 4.9	128 ± 9.7	121 ± 9.0	104 ± 10.7	130 ± 6.0
	10	--	122 ± 10.8	--	--	--	--
	33	89 ± 12.7	118 ± 10.1	125 ± 4.0	--	107 ± 3.2	--
	100	87 ± 3.3	90 ± 5.5	140 ± 14.5	128 ± 15.9	112 ± 10.2	135 ± 4.6
	333	99 ± 2.2	122 ± 14.4	140 ± 13.0	127 ± 5.2	116 ± 3.2	145 ± 11.4
	1,000	66 ± 2.6	76 ± 1.8	139 ± 8.1	122 ± 9.7	130 ± 11.0	114 ± 12.3
	1,666	(d) 0 ± 0.0	--	--	--	--	--
	3,333	--	--	122 ± 5.0	112 ± 8.4	92 ± 4.3	90 ± 9.6
	6,666	--	--	--	(d) 110 ± 10.0	--	(d) 66 ± 1.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	530 ± 25.2	497 ± 38.9	458 ± 84.4	238 ± 17.8	339 ± 69.0	413 ± 11.3
TA1535	0	13 ± 3.2	21 ± 2.0	12 ± 2.0	11 ± 2.0	10 ± 1.5	12 ± 2.3
	10	--	20 ± 2.3	--	--	--	--
	33	17 ± 2.3	23 ± 3.5	9 ± 0.6	--	8 ± 0.3	--
	100	24 ± 2.6	22 ± 2.5	10 ± 0.3	10 ± 1.9	8 ± 2.5	17 ± 1.0
	333	11 ± 4.7	18 ± 1.5	13 ± 1.5	12 ± 0.9	11 ± 1.5	12 ± 2.6
	1,000	10 ± 2.7	14 ± 1.5	13 ± 1.0	13 ± 3.7	6 ± 0.6	15 ± 0.7
	1,666	(d) 2 ± 1.5	--	--	--	--	--
	3,333	--	--	9 ± 0.6	13 ± 1.5	8 ± 1.2	13 ± 2.3
	6,666	--	--	--	8 ± 0.6	--	(d) 12 ± 1.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	267 ± 4.7	332 ± 14.2	168 ± 20.4	310 ± 24.2	198 ± 10.7	100 ± 0.9
TA1537	0	7 ± 3.2	15 ± 2.6	9 ± 1.2	13 ± 2.5	9 ± 2.3	9 ± 3.1
	10	--	7 ± 2.8	--	--	--	--
	33	10 ± 2.9	8 ± 1.0	9 ± 2.8	--	8 ± 0.9	--
	100	7 ± 2.0	9 ± 0.9	10 ± 0.9	13 ± 0.6	9 ± 1.2	7 ± 1.2
	333	5 ± 1.2	8 ± 0.9	10 ± 1.2	10 ± 1.9	7 ± 1.5	5 ± 1.2
	1,000	7 ± 1.2	4 ± 1.5	8 ± 2.0	8 ± 0.7	7 ± 1.2	6 ± 1.5
	1,666	(d) 1 ± 1.3	--	--	--	--	--
	3,333	--	--	7 ± 0.9	7 ± 0.6	7 ± 1.3	6 ± 0.9
	6,666	--	--	--	(d) 11 ± 1.0	--	(d) 5 ± 2.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	301 ± 29.2	376 ± 62.4	50 ± 2.9	49 ± 2.8	43 ± 2.8	56 ± 4.2
TA97	0	132 ± 10.7	157 ± 13.8	152 ± 4.1	166 ± 15.3	140 ± 1.8	194 ± 35.3
	10	--	155 ± 9.0	--	--	--	--
	33	147 ± 4.5	164 ± 12.8	202 ± 3.7	--	168 ± 13.8	--
	100	132 ± 8.6	180 ± 8.7	191 ± 3.2	175 ± 3.8	175 ± 11.5	205 ± 6.4
	333	149 ± 2.0	175 ± 5.9	199 ± 4.0	212 ± 7.1	191 ± 2.1	213 ± 8.3
	1,000	107 ± 0.9	165 ± 5.0	209 ± 0.9	196 ± 16.3	182 ± 11.1	179 ± 16.2
	1,666	(d) 7 ± 7.3	--	--	--	--	--
	3,333	--	--	177 ± 14.1	195 ± 4.1	191 ± 11.2	(d) 184 ± 11.0
	6,666	--	--	--	(d) 192 ± 17.7	--	(d) 103 ± 51.7
	Trial summary	Negative	Negative	Equivocal	Equivocal	Equivocal	Negative
	Positive control (c)	499 ± 49.7	986 ± 88.5	613 ± 20.5	396 ± 6.8	498 ± 3.9	440 ± 6.9

TABLE E1. MUTAGENICITY OF TRIBROMOMETHANE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)							
Study performed at SRI International (Continued)									
		−S9		+S9 (hamster)					
		Trial 1	Trial 2	5%	10%	10%	30%	30%	30%
TA98	0	26 ± 0.7	23 ± 2.0	33 ± 4.5	29 ± 0.3	32 ± 0.9	26 ± 1.5	22 ± 3.3	33 ± 4.6
	10	--	17 ± 0.3	--	--	--	--	--	29 ± 4.3
	33	22 ± 1.7	19 ± 0.9	--	32 ± 2.6	--	--	--	25 ± 2.8
	100	23 ± 3.6	19 ± 2.9	38 ± 5.2	34 ± 7.5	29 ± 2.1	32 ± 4.1	39 ± 0.3	25 ± 4.0
	333	19 ± 2.0	20 ± 3.4	35 ± 1.2	30 ± 6.7	38 ± 1.0	33 ± 1.5	40 ± 1.9	29 ± 3.5
	1,000	12 ± 2.4	11 ± 1.3	32 ± 3.5	37 ± 2.8	34 ± 3.3	39 ± 6.1	41 ± 4.2	30 ± 1.7
	1,666	Toxic	--	--	--	--	--	--	34 ± 2.2
	3,333	--	--	44 ± 3.0	31 ± 5.2	40 ± 2.0	50 ± 3.1	40 ± 4.0	33 ± 1.5
	6,666	--	--	(d) 29 ± 1.3	--	(d) 27 ± 4.5	(d) 51 ± 7.3	(d) 49 ± 2.2	(d) 29 ± 2.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Equivocal	Equivocal	Negative
Positive control (c)		449 ± 16.4	675 ± 40.9	729 ± 26.5	384 ± 45.2	381 ± 24.7	69 ± 3.9	284 ± 5.2	233 ± 30.5

		+S9 (rat)	
		10%	30%
TA98	0	29 ± 2.3	38 ± 3.5
	33	32 ± 1.0	--
	100	31 ± 2.9	30 ± 4.5
	333	27 ± 1.5	33 ± 3.3
	1,000	34 ± 1.0	33 ± 6.4
	3,333	(d) 18 ± 4.2	33 ± 3.5
	6,666	--	(d) 20 ± 0.0
Trial summary		Negative	Negative
Positive control (c)		318 ± 33.8	64 ± 2.0

(a) The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537 and TA97.
(d) Slight toxicity

TABLE E2. MUTAGENICITY OF TRIBROMOMETHANE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
-S9					
Trial 1					
Ethanol (d)		63.5 ± 1.8	100.3 ± 6.2	101.5 ± 5.0	53.5 ± 3.4
Tribromomethane	50	93.0 ± 6.5	133.3 ± 17.6	72.0 ± 15.7	25.3 ± 3.8
	75	76.7 ± 8.6	128.0 ± 10.4	75.3 ± 10.1	34.0 ± 7.0
	100	93.7 ± 14.5	108.3 ± 2.9	105.3 ± 4.3	39.3 ± 5.8
	150	78.3 ± 5.8	99.3 ± 11.2	108.3 ± 6.5	46.7 ± 4.4
	200	86.7 ± 4.2	78.3 ± 3.3	112.0 ± 6.4	43.3 ± 4.1
	250	67.0 ± 7.4	47.3 ± 23.1	157.3 ± 35.8	(e) 84.7 ± 28.8
	300	Lethal	--	--	--
Methyl methanesulfonate	5 µg/ml	84.0 ± 6.0	94.3 ± 6.2	685.0 ± 18.5	(e) 274.7 ± 14.9
Trial 2					
Ethanol (d)		70.3 ± 4.1	100.0 ± 9.8	86.0 ± 7.9	40.5 ± 1.4
Tribromomethane	25	71.7 ± 3.0	112.0 ± 6.7	86.3 ± 17.7	39.7 ± 6.5
	50	68.0 ± 0.6	122.7 ± 14.9	88.3 ± 6.9	43.3 ± 3.5
	100	77.0 ± 4.6	99.0 ± 1.0	108.7 ± 3.4	47.3 ± 1.8
	175	66.7 ± 5.0	35.3 ± 6.7	201.0 ± 19.1	(e) 101.3 ± 6.7
	(f) 200	78.0 ± 10.0	42.0 ± 10.0	183.5 ± 5.5	(e) 79.0 ± 8.0
	(g) 250	60	21	174	97
	300	Lethal	--	--	--
Methyl methanesulfonate	5 µg/ml	62.7 ± 3.9	66.7 ± 15.4	428.7 ± 9.4	(e) 228.7 ± 10.7
Trial 3					
Ethanol (d)		86.0 ± 5.6	100.3 ± 4.3	67.5 ± 3.2	26.5 ± 1.6
Tribromomethane	100	84.0 ± 11.4	49.0 ± 5.5	83.3 ± 10.4	33.3 ± 2.7
	150	83.7 ± 2.0	41.3 ± 3.9	61.7 ± 15.6	25.0 ± 6.4
	(h) 175	63.0 ± 0.0	23.0 ± 6.0	64.5 ± 7.5	34.0 ± 4.0
	200	82.7 ± 4.2	17.3 ± 1.5	133.7 ± 5.7	(e) 54.0 ± 4.0
	225	78.0 ± 2.3	12.3 ± 2.2	105.3 ± 28.7	(e) 45.3 ± 13.1
	(f) 250	71.5 ± 8.5	7.0 ± 2.0	74.0 ± 52.0	32.0 ± 20.0
	300	Lethal	--	--	--
Methyl methanesulfonate (h)	5 µg/ml	48.5 ± 2.5	43.0 ± 5.0	287.5 ± 37.5	(e) 196.0 ± 15.0
+S9 (i)					
Trial 1					
Ethanol (d)		59.0 ± 4.9	100.3 ± 13.3	171.0 ± 8.9	97.8 ± 4.7
Tribromomethane	6.25	56.3 ± 2.2	54.0 ± 3.1	213.3 ± 17.9	126.7 ± 9.0
	12.5	61.3 ± 6.2	27.7 ± 1.3	242.3 ± 19.1	133.0 ± 10.3
	25	52.3 ± 4.9	10.0 ± 0.6	231.7 ± 20.4	(e) 148.7 ± 11.2
	50	Lethal	--	--	--
Methylcholanthrene (h)	2.5 µg/ml	27.5 ± 9.5	4.0 ± 2.0	526.5 ± 90.5	(e) 688.0 ± 135.0

TABLE E2. MUTAGENICITY OF TRIBROMOMETHANE IN MOUSE L5178Y LYMPHOMA CELLS (a,b) (Continued)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
+S9 (Continued)					
Trial 2					
Ethanol (d)		85.3 ± 2.8	100.0 ± 5.1	203.3 ± 13.0	79.5 ± 4.0
Tribromomethane	2.5	68.3 ± 4.2	70.0 ± 7.5	122.7 ± 9.3	60.3 ± 5.9
	5	72.3 ± 4.9	47.7 ± 2.7	146.0 ± 20.7	68.3 ± 11.1
	10	56.7 ± 3.8	26.7 ± 2.0	185.0 ± 35.8	108.0 ± 13.0
	(f) 20	58.0 ± 3.0	13.0 ± 1.0	210.0 ± 37.0	122.5 ± 27.5
	25	59.0 ± 6.0	6.7 ± 1.7	207.7 ± 17.0	(e) 121.7 ± 22.6
	(f) 30	66.0 ± 5.0	7.5 ± 2.5	220.5 ± 16.5	113.0 ± 17.0
Methylcholanthrene	2.5 µg/ml	38.7 ± 4.8	16.0 ± 4.0	850.0 ± 121.4	(e) 736.0 ± 64.9

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the average of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the average of two tests. The dose in one test was lethal.
(g) Data presented are for one test. The dose in two tests was lethal.
(h) Data presented are the average of two tests.
(i) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY TRIBROMOMETHANE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
Study performed at Columbia University								
−S9 (c) Summary: Negative								
Dimethyl sulfoxide		50	1,045	459	0.44	9.2	26	--
Tribromomethane	16	50	1,048	496	0.47	9.9	26.0	107.6
	50	50	1,049	500	0.48	10.0	26.0	108.7
	160	50	1,051	514	0.49	10.3	26.0	112.0
Triethylenemelamine	0.015	50	1,044	1,781	1.71	35.6	26.0	387.0
+S9 (d) Summary: Negative								
Dimethyl sulfoxide		50	1,048	431	0.41	8.6	26.0	--
Tribromomethane	50	50	1,049	461	0.44	9.2	26.0	107.0
	160	50	1,049	498	0.47	10.0	26.0	116.3
	500	50	1,049	493	0.47	9.9	26.0	115.1
Cyclophosphamide	1	50	1,049	1,165	1.11	23.3	26.0	270.9
Study performed at Litton Bionetics, Inc.								
−S9 (c) Summary: Weakly positive								
Dimethyl sulfoxide		50	1,039	427	0.41	8.5	25.5	--
Tribromomethane	29	50	1,034	470	0.45	9.4	25.5	110.6
	96.8	50	1,035	499	0.48	10.0	25.5	117.6
	290	50	1,030	528	0.51	10.6	25.5	124.7
Triethylenemelamine	0.015	50	1,021	3,071	3.01	61.4	25.5	722.4
+S9 (d) Summary: Negative								
Dimethyl sulfoxide		50	1,004	441	0.44	8.8	25.5	--
Tribromomethane	96.8	50	1,025	497	0.48	9.9	25.5	112.5
	290	50	1,020	454	0.45	9.1	(e) 30.5	103.4
	968	50	1,027	531	0.52	10.6	(e) 30.5	120.5
Cyclophosphamide	1.5	50	1,035	1,629	1.57	32.6	25.5	370.5

(a) SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(e) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY TRIBROMOMETHANE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Study performed at Columbia University (d)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3.0		100	3	0.03	3.0
Tribromomethane					Tribromomethane				
50	100	2	0.02	2.0	160	100	4	0.04	3.0
160	100	1	0.01	1.0	500	100	3	0.03	3.0
500	100	0	0.00	0.0	1,600	100	0	0.00	0.0
1,600	100	6	0.06	6.0					
Summary: Negative					Summary: Negative				
Triethylenemelamine					Cyclophosphamide				
0.15	100	34	0.34	25.0	15	100	57	0.57	32.0
Study performed at Litton Bionetics, Inc. (e)									
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0.0		100	0	0.00	0.0
	100	2	0.02	2.0		100	0	0.00	0.0
Tribromomethane					Tribromomethane				
266	100	2	0.02	2.0	266	100	1	0.01	1.0
532	100	2	0.02	2.0	532	100	2	0.02	2.0
1,070	100	6	0.06	6.0	1,070	100	1	0.01	1.0
Summary: Weakly positive					Summary: Negative				
Triethylenemelamine					Cyclophosphamide				
1	100	37	0.37	28.0	25	100	18	0.18	17.0

(a) Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Harvest time, 14.0 hours
(e) Harvest time, 10.5 hours

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY TRIBROMOMETHANE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Injection	1,000	11	18	2/2,027	0/2,009	0/1,650	2/5,686 (0.04%)
	0			0/1,791	2/1,665	4/1,602	6/5,058 (0.12%)
Feeding	3,000	31	4	3/2,212	2/2,139	5/1,809	10/6,160 (0.16%)
	0			1/1,972	1/1,843	1/1,788	3/5,603 (0.05%)

(a) Study performed at University of Wisconsin, Madison. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering et al. (1985). (Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover.) Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE E6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY TRIBROMOMETHANE (a)

Route of Exposure	Dose (ppm)	Transfers Translocations/Total F_1 Tested 1	2	3	4	5	6	Total No. of Tests	Total No. of Translocations	Total Translocations (percent)
Feeding	3,000	0/1,154	0/1,168	0/1,163	0/1,123	0/656	0/116	5,380	0	0
Historical control	0	0/27,245	0/31,611	0/22,410	2/23,623	0/10,506	0/768	116,163	2	0.0017

(a) Study performed at University of Wisconsin, Madison. A detailed protocol of the reciprocal translocation assay is presented in Zimmering et al. (1985). Exposed males were mated to three bw;e females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of six cultures, and then they were discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to bw;e females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE E7. INDUCTION OF SISTER CHROMATID EXCHANGES IN MOUSE BONE MARROW CELLS BY TRIBROMOMETHANE (a)

Compound	Dose (mg/ml)	Mean SCEs/Cell (b)	P Value (c)
Trial 1			
Corn oil		4.4 ± 0.24	
Tribromomethane (d)	200	4.9 ± 0.48	
	400	7.0 ± 1.45	
	800	8.2 ± 0.94	0.0120
Dimethylbenzanthracene (e)	2.5	11.7 ± 0.5	0.0001
Trial 2			
Corn oil		4.5 ± 0.60	
Tribromomethane	800	6.1 ± 0.62	0.0488
Dimethylbenzanthracene (e)	2.5	8.1 ± 0.61	0.0027

(a) Study performed at Brookhaven National Laboratory. Doses are determined by the solubility of the chemical, its lethality in the animals, and/or cell cycle delay induced by chemical exposure. A range-finding study was performed to determine the appropriate dosing regimen. Based on animal mortality, the maximum dose was set at 800 mg/kg. Male B6C3F$_1$ mice (five animals per dose group) were given an intraperitoneal injection of tribromomethane in corn oil (injection volume: 0.4 ml). Solvent control mice received an injection of corn oil only. The positive control mice received an injection of 2.5 mg/kg dimethylbenzanthracene. Twenty-four hours prior to tissue sampling, the mice were subcutaneously implanted with a 50-mg bromodeoxyuridine tablet (McFee et al., 1983), and 2 hours prior to being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Thirty-six (trial 1) or 42 (trial 2) hours after chemical exposure, the animals were killed by cervical dislocation. One or both femurs were removed, and the marrow was flushed out with 5 ml phosphate-buffered saline (pH 7.0). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained by the fluorescence-plus-Giemsa method and scored. Twenty-five second-division metaphase cells were scored from each of four animals per treatment.
(b) Mean ± standard error of the mean; SCE = sister chromatid exchange.
(c) Pairwise comparison between dose group and solvent control group conducted with Student's one-tailed *t*-test.
(d) Trend P value = 0.0018 by a one-tailed trend test used to determine if dose-related increase is present (Margolin et al., 1986)
(e) Positive control

TABLE E8. INDUCTION OF CHROMOSOMAL ABERRATIONS IN MOUSE BONE MARROW CELLS BY TRIBROMOMETHANE (a)

Compound	Dose (mg/kg)	Aberrations/Cell (b)	Damaged Cells (b) (percent)
Corn oil		0.01 ± 0.005	1.00 ± 0.535
Tribromomethane	(c) 200	0.02 ± 0.008	2.29 ± 0.808
	400	0.03 ± 0.012	3.25 ± 1.250
	800	0.02 ± 0.009	2.00 ± 0.926
Trend P value (d)		0.2846	0.2486
Dimethylbenzanthracene (e)	100	0.48 ± 0.140	18.00 ± 2.976

(a) Study performed at Brookhaven National Laboratory. Doses are determined by the solubility of the chemical, its lethality in animals, and/or cell cycle delay induced by chemical exposure. A range-finding study was performed to determine the appropriate dosing regimen. Based on animal mortality, the maximum dose was set at 800 mg/kg. Male B6C3F_1 mice (10 animals per dose group) were given an intraperitoneal injection of tribromomethane in corn oil (injection volume: 0.4 ml). Solvent control mice received an injection of corn oil only. The positive control mice received an injection of 100 mg/kg dimethylbenzanthracene. Twenty-four hours later, the mice were subcutaneously implanted with a 50-mg bromodeoxyuridine (BrdU) tablet (McFee et al., 1983). BrdU was used to allow selection of the appropriate cell population for scoring. (Chemically induced chromosomal aberrations are present in maximum number at the first metaphase after exposure; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before being killed, the mice received an intraperitoneal injection of 2 mg/kg colchicine (in saline). Thirty-six hours after chemical exposure (12 hours after BrdU dosing), the animals were killed by cervical dislocation. One or both femurs were removed, and the marrow was flushed out with 5 ml phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. Following a 24-hour drying period, the slides were stained and scored. Fifty first-division metaphase cells were scored from each of eight animals per treatment (unless otherwise specified). Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The number of aberrations per cell (excluding gaps) was also analyzed to provide information on the extent of individual cell damage.
(b) Mean ± standard error of the mean
(c) Number of animals: 7
(d) One-tailed trend test used to determine if dose-related increase is present (Margolin et al., 1986)
(e) Positive control

TABLE E9. INCIDENCE OF MICRONUCLEI IN BONE MARROW POLYCHROMATIC ERYTHROCYTES OF B6C3F$_1$ MICE EXPOSED TO TRIBROMOMETHANE (a)

Dose (mg/kg)	Micronucleated PCEs/ 1,000 Cells (b)	Number of Animals	P Value
Tribromomethane			
0	2.60 ± 0.427	10	(c) 0.0095
200	2.90 ± 0.482	10	
400	3.10 ± 0.482	10	
800	4.40 ± 0.748	10	
Dimethylbenzanthracene (d)			
100	31.50 ± 3.291	10	(e) 0.0001

(a) PCE = polychromatic erythrocyte. Doses are determined by solubility of the chemical and animal lethality and/or cell cycle delay induced by chemical exposure. Male mice were injected intraperitoneally with tribromomethane dissolved in corn oil twice at 24-hour intervals. Vehicle control mice received injections of corn oil only. The positive control mice received injections of dimethylbenzanthracene. Twenty-four hours after the second injection, mice were killed by cervical dislocation, and smears were prepared of the bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 1,000 polychromatic erythrocytes were scored for frequency of micronuclei in each of 10 animals per dose group.
(b) Mean ± standard error of the mean of the pooled results from all animals scored within a dose group
(c) One-tailed trend test used to determine if treatment-related increase is present (Margolin et al., 1986)
(d) Positive control
(e) Pairwise comparison between dose group and corresponding solvent control group conducted with Student's one-tailed *t*-test

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect 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 viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

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

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIBROMOMETHANE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	8/10	RCV
12	9/10	RCV
	(b) 1/10	Sendai
18	4/10	KRV
	8/10	RCV
24	8/10	RCV
	3/10	KRV
MICE		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) May be considered a false positive

APPENDIX G

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Meal Diet: December 1980 to January 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE G1. 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, 1976b; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE G2. VITAMINS AND MINERALS IN NIH 07 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 G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.25 ± 1.04	22.6-26.3	24
Crude fat (percent by weight)	5.10 ± 0.44	4.4-6.0	24
Crude fiber (percent by weight)	3.38 ± 0.38	2.4-4.2	24
Ash (percent by weight)	6.59 ± 0.34	5.97-7.42	24
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,188 ± 1,239	8,900-14,000	24
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.2 ± 2.3	12.0-21.0	(b) 23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.23 ± 0.12	1.10-1.53	24
Phosphorus (percent)	0.97 ± 0.06	0.84-1.10	24
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured during 1983-85.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.14	<0.21-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.03 ± 0.75	0.27-2.93	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.27 ± 0.05	0.16-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	24
Nitrate nitrogen (ppm) (c)	9.35 ± 4.35	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	1.97 ± 1.28	0.4-5.3	24
BHA (ppm) (d)	5.83 ± 5.12	0.4-20.0	24
BHT (ppm) (d)	3.42 ± 2.57	<1.0-13.0	24
Aerobic plate count (CFU/g) (e)	105,438 ± 75,797	7,000-300,000	24
Coliform (MPN/g) (f)	1,046 ± 973	<3-2,400	24
E. coli (MPN/g) (g)	8.0 ± 7.91	<3-23	23
E. coli (MPN/g) (h)	13.92 ± 30.00	<3-150	24
Total nitrosamines (ppb) (i,j)	5.13 ± 4.47	<1.2-18.8	22
Total nitrosamines (ppb) (i,k)	13.11 ± 27.39	<1.2-101.6	24
N-Nitrosodimethylamine (ppb) (i,l)	3.82 ± 4.29	0.6-16.8	22
N-Nitrosodimethylamine (ppb) (i,m)	11.71 ± 27.03	0.6-99	24
N-Nitrosopyrrolidine (ppb)	1.21 ± 0.66	<0.3-2.4	24
Pesticides (ppm)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (o)	<0.01	0.05 (7/14/81)	24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (p)	<0.05	0.13 (8/25/81); 0.6 (6/29/82)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (q)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (a,r)	<0.01		14
Endosulfan II (a,r)	<0.01		14
Endosulfan sulfate (a,r)	<0.03		14

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one value of 150 obtained for the batch produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value listed in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb obtained for batches produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the very high values given in (j).
(l) Mean, standard deviation, and range exclude the very high values of 97.9 and 99 obtained for batches produced on 1/26/81 and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(p) There were two observations above the detection limit; the values and dates they were obtained are given under the range.
(q) Eleven batches contained more than 0.05 ppm.
(r) Analysis started on 12/23/81

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and preliminary draft (August 1987) of NTP Technical Report No. 350 for the 2-year studies of tribromomethane in rats and mice were audited for the NIEHS at the NTP Archives during August 1987 by Argus Research Laboratories, Inc. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of animals in all study groups, plus other relevant cases to verify animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group to examine for proper match and inventory.
(8) All red-lined diagnoses on the intermediate pathology table to verify incorporation of changes into the final tables.
(9) Correlation between the data, results, and procedures for the 2-year studies presented in the preliminary draft of the Technical Report and the records available at the NTP Archives.

The audit showed that inlife procedures and events were documented by archival records with some minor exceptions. The disposition of surplus animals; frequency for changing feeders, cages, and racks; twice daily cage checks; light cycle checks; and airflow exchange measurements were not documented other than in the laboratory's final report. Doses were prepared and administered to animals properly except for two overdosing incidents that were documented properly. Of the masses noted in the inlife records, 61/63 in rats and 89/94 in mice were correlated with necropsy observations.

Audit of the pathology specimens showed that identifiers (punched ears) were present and correct in the tissue bags for 64/65 rats and 67/67 mice examined. The ear of one rat had one marking removed so that a potential lesion could be processed for histopathologic examination. Tissue bags were absent for two mice. The audit identified untrimmed potential lesions in nontarget organs in one rat and one mouse and found that the gastrointestinal tract was not cut open or only partially opened in the majority of animals examined. Consequently, the intestines of all rats and mice in these studies were examined grossly, and sections of untrimmed potential neoplasms were evaluated. These results are included in this Technical Report. Other audit findings were reviewed and judged to have no adverse impact on interpretation of the pathology data.

Full details about these and other audit findings are presented in the audit reports, which are on file at the NIEHS. In conclusion, the data and results presented in the draft Technical Report for the 2-year gavage studies of tribromomethane are supported by the records at the NTP Archives.

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