NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIBROMOACETIC ACID

(CAS NO. 631-64-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

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

April 2007

NTP TR 537

NIH Publication No. 07-4475

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

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CONTENTS

SUMMARY

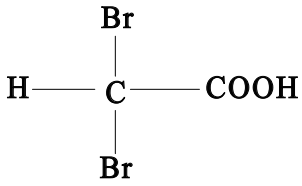
Background
Dibromoacetic acid occurs as a by-product of chlorination of drinking water. We studied the effects of dibromoacetic acid in drinking water on male and female rats and mice to identify potential toxic or cancer-related hazards.

Methods
We gave drinking water containing 50, 500 or 1,000 mg of dibromoacetic acid per liter of water to groups of 50 male and female rats and mice for 2 years. Control animals received the same tap water with no chemical added. At the end of the study, tissues from more than 40 sites were examined for every animal.

Results
Survival was similar for animals receiving dibromoacetic acid and the controls. Male rats receiving dibromoacetic acid had increased rates of malignant mesotheliomas. The rates of mononuclear cell leukemia increased in exposed female rats and, to a lesser extent, in exposed male rats. Male and female mice exposed to dibromoacetic acid had increased rates of a variety of liver cancers, and lung tumors were increased in male mice and, to a lesser extent, in female mice.

Conclusions
We conclude that dibromoacetic acid in the drinking water caused mesothelioma in male rats and mononuclear cell leukemia in female rats, and also possibly in male rats. We conclude that dibromoacetic acid caused liver cancer in male and female mice and lung cancer in male, and possibly also in female mice.

ABSTRACT



DIBROMOACETIC ACID

CAS No. 631-64-1

Chemical Formula: $C_2H_2Br_2O_2$ Molecular Weight: 217.86

Synonyms: Acetic acid, dibromo (9CI); dibromoethanoic acid; dibromoacetate

Dibromoacetic acid is a water disinfection by-product. Dibromoacetic acid was nominated to the National Toxicology Program by the United States Environmental Protection Agency for toxicity and carcinogenicity studies in rats and mice because of widespread human exposure and because a related dihaloacetate, dichloroacetate, was found to be carcinogenic to the liver of rats and mice. Drinking water was selected as the route of exposure to mimic human exposure to this chemical. Male and female F344/N rats and B6C3F$_1$ mice were exposed to dibromoacetic acid (greater than 99% pure) in drinking water for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and peripheral blood erythrocytes of exposed mice.

2-Week Study in Rats

Groups of five male and five female rats were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg/L dibromoacetic acid in drinking water for 2 weeks, equivalent to average daily doses of approximately 17, 32, 67, 134, 270 (males), or 257 (females) mg dibromoacetic acid/kg body weight. All rats survived to the end of the study. Mean body weight gains of 1,000 mg/L males and of 500 mg/L females were significantly greater than those of the controls. Water consumption by exposed and control groups was similar. Liver weights of exposed males and females were significantly increased. Right testis weights of males exposed to 500 mg/L or greater were significantly decreased. The incidences of hepatocytic cytoplasmic alteration were significantly increased in males exposed to 500 mg/L or greater and in 2,000 mg/L females. Testicular lesions, characterized by a delay in spermiation and retained spermatids, were noted in males exposed to 500 mg/L or higher concentrations.

2-Week Study in Mice

Groups of five male and five female mice were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg/L dibromoacetic acid (equivalent to average daily doses of approximately 24, 47, 95, 178, or 370 mg/kg to males and 22, 53, 88, 166, or 309 mg/kg to females) in drinking water for 2 weeks. All mice survived to the end of the study. Mean body weight gains of 250 and 500 mg/L males were significantly greater than those of the controls. Water consumption by exposed and control groups was similar. Liver weights of males and females in the 1,000 and 2,000 mg/L groups were significantly increased. Thymus weights of males and females in the 1,000 and 2,000 mg/L groups were significantly less than those of controls. The incidences of thymus atrophy were significantly increased in 1,000 and 2,000 mg/L males

and 2,000 mg/L females. The incidences of morphological changes to the germinal epithelium of the testes were increased in males exposed to 1,000 or 2,000 mg/L.

3-Month Study in Rats

Groups of 10 male and 10 female rats were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg/L dibromoacetic acid (equivalent to average daily doses of approximately 10, 20, 40, 90, and 166 mg/kg to males and 12, 23, 48, 93, and 181 mg/kg to females) in drinking water for 3 months. All rats survived to the end of the study. Mean body weights of male and female rats in the 2,000 mg/L group were significantly less than those of controls. Water consumption by the 2,000 mg/L males at weeks 1 and 13 and by females at week 13 was less than that by controls. Small decreases in the erythron and platelet counts occurred in rats exposed to 2,000 mg/L; minimally impaired erythropoiesis was also seen in 1,000 mg/L rats. Liver weights of all exposed groups of males and females were significantly increased. Male rats in the 2,000 mg/L group had significantly decreased testis weights. Testicular atrophy was noted in the 2,000 mg/L group, and retained spermatids were observed in the 500 and 1,000 mg/L groups. In the pituitary gland of male rats exposed to 2,000 mg/L, the incidence of cellular hypertrophy was significantly increased. The incidences of hepatocellular vacuolization were significantly increased in males exposed to 500 mg/L or greater and in females exposed to 2,000 mg/L. Hematopoietic cell proliferation was noted in females in the 2,000 mg/L group.

3-Month Study in Mice

Groups of 10 male and 10 female mice were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg/L dibromoacetic acid (equivalent to average daily doses of approximately 16, 30, 56, 115, and 230 mg/kg to males and 17, 34, 67, 132, and 260 mg/kg to females) in drinking water for 3 months. All mice survived to the end of the study. Mean body weights and body weight gains of female mice in the 2,000 mg/L group and the mean body weight gain of 2,000 mg/L males were significantly less than those of controls. Water consumption by males in the 2,000 mg/L group was decreased at weeks 1 and 13 relative to controls. Small decreases in mean cell hemoglobin and platelet counts occurred in 2,000 mg/L male mice. Liver weights of males and females exposed to 500 mg/L or greater were significantly increased. Hepatocellular cytoplasmic vacuolization was present in most mice, and the severity was increased in 1,000 and 2,000 mg/L males and females. The incidences of abnormal testicular morphology were significantly increased in 1,000 and 2,000 mg/L males.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to drinking water containing 0, 50, 500, and 1,000 mg/L dibromoacetic acid for 2 years (equivalent to average daily doses of approximately 2, 20, and 40 mg/kg to males and 2, 25, and 45 mg/kg to females). Survival of exposed rats was similar to that of the control groups. Mean body weights of 1,000 mg/L males and females were less than those of the controls after weeks 29 and 53, respectively, and those of 500 mg/L males and females were less after weeks 57 and 85, respectively. Water consumption by males and females exposed to 1,000 mg/L was less than that by controls during year 2 of the study.

The incidence of malignant mesothelioma was significantly increased in 1,000 mg/L male rats. A positive trend in the incidence of mononuclear cell leukemia occurred in female rats, and the incidence in 1,000 mg/L females was significantly increased. The incidences of mononuclear cell leukemia were increased in 50 and 500 mg/L males. The incidences of cystic degeneration of the liver were significantly increased in all exposed groups of male rats. The incidences of alveolar epithelial hyperplasia were significantly increased in 500 and 1,000 mg/L females, and the incidences of nephropathy were significantly increased in all exposed groups of females.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to drinking water containing 0, 50, 500, and 1,000 mg/L dibromoacetic acid for 2 years (equivalent to average daily doses of approximately 4, 45, and 87 mg/kg to males and 4, 35, and 65 mg/kg to females). Survival of exposed mice was similar to that of the controls. Mean body weights of 50 and 500 mg/L male mice were greater than those of the controls after week 85. Water consumption by exposed mice was generally similar to that by controls throughout the study.

The incidences of liver neoplasms occurred with positive trends in male and female mice. The incidences of multiple hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all exposed groups of males and in 500 and 1,000 mg/L females. The incidences of hepatoblastoma were significantly increased in 500 and 1,000 mg/L males, and the incidences of hepatocellular carcinoma were significantly increased in 1,000 mg/L males and 500 mg/L females. The incidences of alveolar/bronchiolar adenoma occurred with positive trends in males and females, and the incidence in 500 mg/L male mice was significantly greater than that in controls.

Genetic Toxicology

Dibromoacetic acid was mutagenic in *Salmonella typhimurium* strain TA100 with or without rat or hamster liver metabolic activation enzymes (S9); no activity was detected in strain TA98, with or without S9. Increased frequencies of micronucleated normochromatic erythrocytes were observed in peripheral blood samples from male, but not female, mice administered dibromoacetic acid in drinking water for 3 months.

Conclusions

Under the conditions of these studies, there was *some evidence of carcinogenic activity** of dibromoacetic acid in male rats based on an increased incidence of malignant mesothelioma. The increased incidences of mononuclear cell leukemia in male rats may have been related to dibromoacetic acid exposure. There was *some evidence of carcinogenic activity* of dibromoacetic acid in female rats based on an increased incidence and positive trend of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of dibromoacetic acid in male and female mice based on increased incidences of hepatocellular neoplasms and hepatoblastoma (males only). Increased incidences of lung neoplasms in male mice were also considered to be exposure related. The slight increased incidence of lung neoplasms in female mice may have been related to dibromoacetic acid exposure.

Exposure to dibromoacetic acid for 2 years caused increased incidences of cystic degeneration of the liver in male rats, increased incidences of alveolar epithelial hyperplasia and nephropathy in female rats, and increased incidences of splenic hematopoiesis in male mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Dibromoacetic Acid

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in drinking water	0, 50, 500, or 1,000 mg/L	0, 50, 500, or 1,000 mg/L	0, 50, 500, or 1,000 mg/L	0, 50, 500, or 1,000 mg/L
Body weights	500 and 1,000 mg/L groups less than the control group	1,000 mg/L group less than the control group	50 and 500 mg/L groups greater than the control group	Exposed groups similar to the control group
Survival rates	34/50, 24/50, 30/50, 28/50	35/50, 39/50, 35/50, 32/50	31/50, 38/50, 34/50, 31/50	38/50, 35/50, 32/50, 32/50
Nonneoplastic effects	Liver: degeneration, cystic (3/50, 9/50, 11/50, 15/50)	Lung: alveolar epithelium, hyperplasia (3/50, 7/50, 13/50, 14/50) Kidney: nephropathy (18/50, 32/50, 37/50, 40/50)	Spleen: hematopoiesis (18/49, 20/50, 28/50, 38/50)	None
Neoplastic effects	All organs: malignant mesothelioma (3/50, 1/50, 0/50, 10/50)	All organs: mononuclear cell leukemia (11/50, 13/50, 16/50, 22/50)	Liver: hepatocellular adenoma (18/49, 37/50, 37/50, 42/50); hepatocellular carcinoma (14/49, 9/50, 19/50, 26/50); hepatocellular adenoma or carcinoma (28/49, 41/50, 42/50, 47/50); hepatoblastoma (0/49, 4/50, 6/50, 18/50) Lung: alveolar/bronchiolar adenoma (7/49, 5/50, 17/50, 12/50); alveolar/bronchiolar adenoma or carcinoma (12/49, 12/50, 22/50, 17/50)	Liver: hepatocellular adenoma (19/49, 26/50, 32/50, 35/49); hepatocellular carcinoma (3/49, 3/50, 12/50, 8/49); hepatocellular adenoma or carcinoma (22/49, 28/50, 37/50, 37/49)
Equivocal findings	All organs: mononuclear cell leukemia (17/50, 31/50, 24/50, 13/50)	None	None	Lung: alveolar/bronchiolar adenoma (1/50, 3/50, 3/50, 6/50); alveolar/bronchiolar adenoma or carcinoma (2/50, 5/50, 5/50, 7/50)
Level of evidence of carcinogenic activity	Some evidence	Some evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Positive in TA100 with and without S9; negative in TA98 with or without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo:*	Positive in males; negative in females			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on dibromoacetic acid on September 27-28, 2005, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 27, 2005, the draft Technical Report on the carcinogenesis studies of dibromoacetic acid received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.L. Melnick, NIEHS, described the occurrence of dibromoacetic acid as a water disinfection by-product, the design and results of the NTP studies, and the metabolism and a pharmacokinetic model for the behavior of the chemical in rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* of dibromoacetic acid in male and female rats and *clear evidence of carcinogenic activity* of dibromoacetic acid in male and female mice. Increased incidences of lung neoplasms in male mice were also considered to be exposure related. The slight increased incidence of lung neoplasms in female mice may have been related to dibromoacetic acid exposure.

Dr. Walker, a principal reviewer, was unable to attend the meeting. Dr. Vore, the second principal reviewer, felt the study was well conducted and reported, and she agreed with the proposed conclusions. Dr. Elwell asked for more explanation of the reasons for classifying the mononuclear cell leukemia in female rats as *some evidence* and noted that rather similar values formed the basis of an *equivocal evidence* call in a different study presented at this review. Dr. Crump noted another study where a similar increase in mononuclear cell leukemia was considered *no evidence*. Drs. Roberts and Vore also expressed a desire for consistency in making conclusions and commented on the variability of the occurrence of mononuclear cell leukemia in rats.

Dr. J.R. Bucher, NIEHS, urged that the panel consider each study as unique and base the conclusions on that study rather than comparing incidences in studies conducted separately.

Dr. C.J. Portier, NIEHS, and Dr. Roberts both commented on the high rates of mononuclear cell leukemia in the low- and mid-dose groups of male rats.

Dr. Vore moved and Dr. Roberts seconded that the conclusion for male rats be modified to add that mononuclear cell leukemia "may have been related to chemical exposure." The motion was carried with five affirmative votes and one negative (Dr. Elwell).

The following day, on September 28, 2005, following review of the other reports for this peer review meeting, including two studies involving conclusions based on mononuclear cell leukemia in female rats, Dr. Roberts asked that the panel revisit the conclusions for dibromoacetic acid to ensure that conclusions from studies were being considered consistently. The attendance was the same as on September 27, except that Dr. Birt was not present.

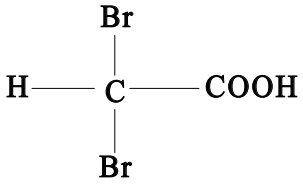
Dr. Bucher restated the arguments for calling the female rat leukemia response *some evidence*, including a statistically significant trend, a doubling of the incidence in the high-dose group, and the concurrent control group matching the historical control mean.

Dr. Roberts asked why the conclusion was different from that proposed for the 4-methylimidazole study and suggested *equivocal evidence* might be more appropriate. Dr. Elwell noted that the statistical support was slightly stronger for the 4-methylimidazole female rats. Dr. Crump suggested the historical range from only four drinking water studies might be artificially tight, given the variability seen in other studies. Dr. Soper also suggested *equivocal evidence* might be more appropriate.

Dr. Portier noted that the concurrent control incidence in the 4-methylimidazole study was lower than in the dibromoacetic acid study, which was close to the historical mean.

Dr. Melnick reported having consulted reports of some previously printed Technical Reports where mononuclear cell leukemia contributed to *some evidence* conclusions. He described the incidences of mononuclear cell leukemia in the study of C.I. Disperse Blue 1, where the lesion was part of the conclusion of *clear evidence*. Following further discussion, no motion was made to revise the conclusions approved the previous day. The panel recommended enhanced discussion of the supporting logic for the conclusions.

INTRODUCTION



DIBROMOACETIC ACID

CAS No. 631-64-1

Chemical Formula: $C_2H_2Br_2O_2$ Molecular Weight: 217.86

Synonyms: Acetic acid, dibromo (9CI); dibromoethanoic acid; dibromoacetate

Chemical and Physical Properties

Dibromoacetic acid is a deliquescent crystal (melting point, 48° C; boiling point, 195° C at 250 mm mercury) (Weast, 1983). It is a moderately strong acid, having a pK_a of 1.39 (Urbansky, 2000). In dilute solutions at pH greater than 6, more than 99.99% of the chemical exists as the dissociated carboxylate anion, dibromoacetate. Thus, under most conditions of exposure, and in biological tissues, this chemical exists as the carboxylate anion. Although dibromoacetic acid was the test article for this Technical Report, in the animal, it is described as dibromoacetate after it leaves the stomach.

Production, Use, and Human Exposure

Chloroacetates are formed when drinking water supplies containing natural organic matter (e.g., humic or fulvic acids) are disinfected with chlorine-containing oxidizing compounds such as chlorine gas, hypochlorous acid, and hypochlorite. If bromide is present in the source water, it may be oxidized to hybromous acid-hypobromite ion, which can react with organic matter to form brominated organic compounds. The reaction of brominated and/or chlorinated oxidizing agents with natural organic matter produces mixed brominated and chlorinated acetic acids, including mono-, di-, and trichloroacetic acid; mono-, di-, and tribromoacetic acid; bromochloroacetic acid; bromodichloroacetic acid; and chlorodibromoacetic acid. The relative amount of brominated haloacetates produced in chlorinated drinking water is a function of the bromide concentration in the source water and the initial bromine/chlorine ratio.

Coagulation prior to chlorination removes much of the disinfection by-product precursors from source water and thereby reduces the amount of disinfection by-products formed during disinfection. Although possible reactions of haloacetates in water are decarboxylation and nucleophilic substitution (hydrolysis), these processes are very slow in ambient water, and most decreases in concentrations of haloacetates in drinking water distribution systems are likely due to biodegradation (Urbansky, 2001).

Haloacetates are second to trihalomethanes as the most commonly detected disinfection by-products in surface drinking water supplies in the United States (Liang and Singer, 2003). The relative amounts of these two families of chemicals as well as other disinfection by-products produced in drinking water supplies are affected by the nature and concentration of the organic precursor materials, water temperature, pH, the type of disinfectant, the disinfectant dose, and contact time

(Liang and Singer, 2003; Huang *et al.*, 2004). For example, increasing the pH from 6 to 8 increases trihalomethane formation, decreases trihaloacetate formation, and has little effect on mono- and dihaloacetate levels. Bromoform and dibromoacetate were the predominant disinfection by-products measured in water from the Sea of Galilee (approximately 2 mg bromide/L) that was pretreated with chlorination for algae control and then disinfected with chlorine dioxide and chloramines (Richardson *et al.*, 2003). Controlled laboratory studies also showed that dibromoacetate is produced by chlorine dioxide treatment (Richardson *et al.*, 2003) or ozonation (Huang *et al.*, 2004) of water containing high ambient bromide concentrations.

Levels of haloacetic acids in drinking water are regulated by the United States Environmental Protection Agency (40 CFR, § 141.64). Under the disinfection by-product rule, the sum of monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, and dibromoacetic acid is limited to 60 µg/L (60 ppb). This level is believed to reduce risks from cancer as well as reproductive and developmental toxicity. A nationwide study of disinfection by-product occurrence in diverse geographic regions of the United States was conducted between October 2000 and April 2002 (Weinberg *et al.*, 2002). In this study, 12 water treatment plants that had different source water quality and bromide levels and that employed the major disinfectants chlorine, chloramines, ozone, and chlorine dioxide were sampled quarterly. Concentrations of dibromoacetate in the finished water ranged up to 18 µg/L and estimates of dibromoacetate concentration in the distribution systems ranged up to 22 µg/L.

Much higher levels of human exposure to dichloroacetate have occurred from therapeutic use of this agent to treat lactic acidosis; dichloroacetate acts by stimulating the mitochondrial pyruvate dehydrogenase complex, resulting in increased oxidation of glucose, lactate, and pyruvate (Stacpoole *et al.*, 1998). Dichloroacetate is also a metabolite of trichloroethylene. Health effects of dichloroacetate may be relevant to dibromoacetate because of qualitative similarities in the metabolism of the chlorinated/brominated dihaloacetates.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Dihaloacetates are rapidly absorbed from the gastrointestinal tract after oral exposure. The maximum blood concentration of dibromoacetate in F344/N rats was reached 1 hour after administration by gavage (Schultz *et al.*, 1999).

Dihaloacetates exhibit low binding to rat plasma proteins (Schultz *et al.*, 1999). Forty-eight hours after oral administration of ^{14}C-dichloroacetate in male F344/N rats, 5% to 8% of administered radiolabel was measured in the liver, 5% to 10% in muscle, 3.3% to 4.5% in skin, 1.4% to 2.6% in blood, and 1.0% to 1.7% in the intestines (Lin *et al.*, 1993). Dibromoacetate was measured in the testicular interstitial fluid of male Sprague-Dawley rats given five daily gavage doses of 250 mg dibromoacetate/kg body weight (Holmes *et al.*, 2001). The level of dibromoacetate in testicular fluid peaked at 79 µg/mL (approximately 370 µM) 30 minutes after the last dose, and the half-life was approximately 1.5 hours. Dibromoacetate was administered to Sprague-Dawley rats in drinking water at concentrations ranging from 125 to 1,000 ppm (mg/L) with exposures beginning 14 days before cohabitation and continuing through gestation and lactation (Christian *et al.*, 2001). Quantifiable levels of dibromoacetate were measured in parental and fetal plasma, placental tissue, amniotic fluid, and milk. Thus, dibromoacetate crosses the placenta and is taken up by fetal tissue.

The oral bioavailability of dibromoacetate was reported to be 30% in male F344/N rats (Schultz *et al.*, 1999). The lower bioavailability of dibromoacetate compared to dichloroacetate is due to greater first-pass metabolism of dibromoacetate in the liver. Biotransformation of dihaloacetates to glyoxylate occurs primarily in liver cytosol of rats and humans by a glutathione-dependent process (James *et al.*, 1997) catalyzed by glutathione-*S*-transferase$_{zeta}$ (GSTζ) (Tong *et al.*, 1998a). This enzyme also catalyzes the penultimate step in the tyrosine degradation pathway. Glyoxylate is the only stable metabolite of dichloroacetate formed by purified GSTζ (Tong *et al.*, 1998b). The major metabolites identified in the urine or blood of F344/N rats or B6C3F$_1$ mice administered dichloroacetate are glyoxylate, glycolate, and oxalate (Lin *et al.*, 1993; Narayanan *et al.*, 1999).

In addition to these metabolites, approximately 30% of radioactivity from orally administered ^{14}C-dichloroacetic acid was exhaled as carbon dioxide (Lin *et al.*, 1993; Xu *et al.*, 1995). Mice metabolize dichloroacetate at approximately twice the rate of rats (Gonzalez-Leon *et al.*, 1999).

During GSTζ-mediated oxygenation of dichloroacetate or other dihaloacetates to glyoxylate, glutathione is required but not consumed. The reaction scheme for the GSTζ-mediated biotransformation of dihaloacetates (Figure 1) involves displacement of a halide by glutathione to form *S*-(α-halocarboxymethyl)glutathione, hydrolysis of this intermediate to form *S*-(α-hydroxycarboxymethyl)glutathione, and elimination of glutathione to produce glyoxylate (Tong *et al.*, 1998b). Among the brominated/chlorinated dihaloacetates, the relative rates of glyoxylate formation catalyzed by purified GSTζ are bromochloroacetate > dichloroacetate > dibromoacetate. In an interspecies comparison of the kinetics of dichloroacetate metabolism, the K_m with human liver cytosol was smaller than that with rat or mouse cytosol; however, the relative rates of metabolism to glyoxylate (V_{max}/K_m) were mouse > rat > human (Tong *et al.*, 1998b). Glyoxylate can undergo transamination to glycine, decarboxylation to form carbon dioxide, and oxidation to oxalate.

After gavage administration, elimination of dichloroacetate in rats occurs by exhalation as carbon dioxide and excretion of metabolites in the urine (Lin *et al.*, 1993). Elimination half-lives of dihaloacetates in blood are less than 4 hours; for dibromoacetate, the plasma half-life after intravenous injection is approximately 30 to 40 minutes (Schultz *et al.*, 1999). Elimination of dihaloacetates is primarily by metabolism; less than 3% of an intravenous dose (500 µmol dibromoacetate/kg body weight; 109 mg/kg) is excreted as the parent compound in urine and less than 0.1% is eliminated in feces. Bromine substitution of dihaloacetates increases the rate of metabolic clearance; dichloroacetate is cleared at half the rate of dibromoacetate. Pretreatment of male F344/N rats with 0.2 or 2.0 g dichloroacetate/L drinking water for 2 weeks reduced the rate of metabolic clearance of subsequent intravenous or gavage doses of dichloroacetate by sixfold (Gonzalez-Leon *et al.*, 1997). In addition, pretreatment caused increased blood concentration-time profiles and elimination half-lives for dichloroacetate, decreased formation of carbon dioxide, and increased renal excretion of dichloroacetate. Dichloroacetate pretreatment also inhibited the conversion of dichloroacetate to glyoxylate, oxalate, or glycolate in hepatic cytosol.

Metabolic clearance of dichloroacetate was also decreased in male B6C3F$_1$ mice pretreated with 2 g dichloroacetate/L drinking water for 14 days; however, the effect in mice was less marked than that in rats (Gonzalez-Leon *et al.*, 1999). Pretreatment of male B6C3F$_1$ mice with 1 g dichloroacetic acid/L drinking water for 2 weeks resulted in a threefold decrease in the rate of metabolism of dichloroacetate in liver cytosol, and similar reduction in the rate of formation of glyoxylate, oxalate, and glycolate (Austin and Bull, 1997). Elimination of dichloroacetate in children or adults is also reduced as a result of prior exposure to therapeutic doses of this agent (Curry *et al.*, 1991; Stacpoole *et al.*, 1998). The reduced elimination of dichloroacetate in pretreated animals is due to irreversible inactivation of GSTζ; the degradation rate constant for GSTζ in the liver of male F344/N rats given five daily intraperitoneal injections of 0.30 mmol dichloroacetate/kg body weight (38 mg/kg) is 0.21/day (Anderson *et al.*, 1999). Treatment of male F344/N rats with 0.2 g dichloroacetate/L drinking water for 7 days reduces liver GSTζ activity by 90%; this reduction markedly decreases the metabolic elimination of dichloroacetate and increases its oral bioavailability (Saghir and Schultz, 2002).

Dibromoacetate and bromochloroacetate are also suicide substrates for GSTζ; 12 hours after a single injection of these dihaloacetates, GSTζ activity in the rat liver is reduced to 17% and 19%, respectively, of that in controls. Hydrolysis of *S*-(α-halocarboxymethyl)glutathione forms a hemithioacetal that eliminates glutathione and yields glyoxylate; however, this intermediate may inactivate GSTζ by covalently binding to a nucleophilic site on the enzyme (Wempe *et al.*, 1999). Thus, hydrolysis of this intermediate and inactivation of GSTζ are competing reactions. Based on the differential effect of dichloroacetate-induced inactivation of GSTζ on the elimination of (+)-bromochloroacetate versus (-)-bromochloroacetate in male F344/N rats, Schultz and Sylvester (2001) suggested that an additional GST isoenzyme that is not inactivated by dihaloacetates might provide a minor contribution to the formation of glyoxylate in non-pretreated animals.

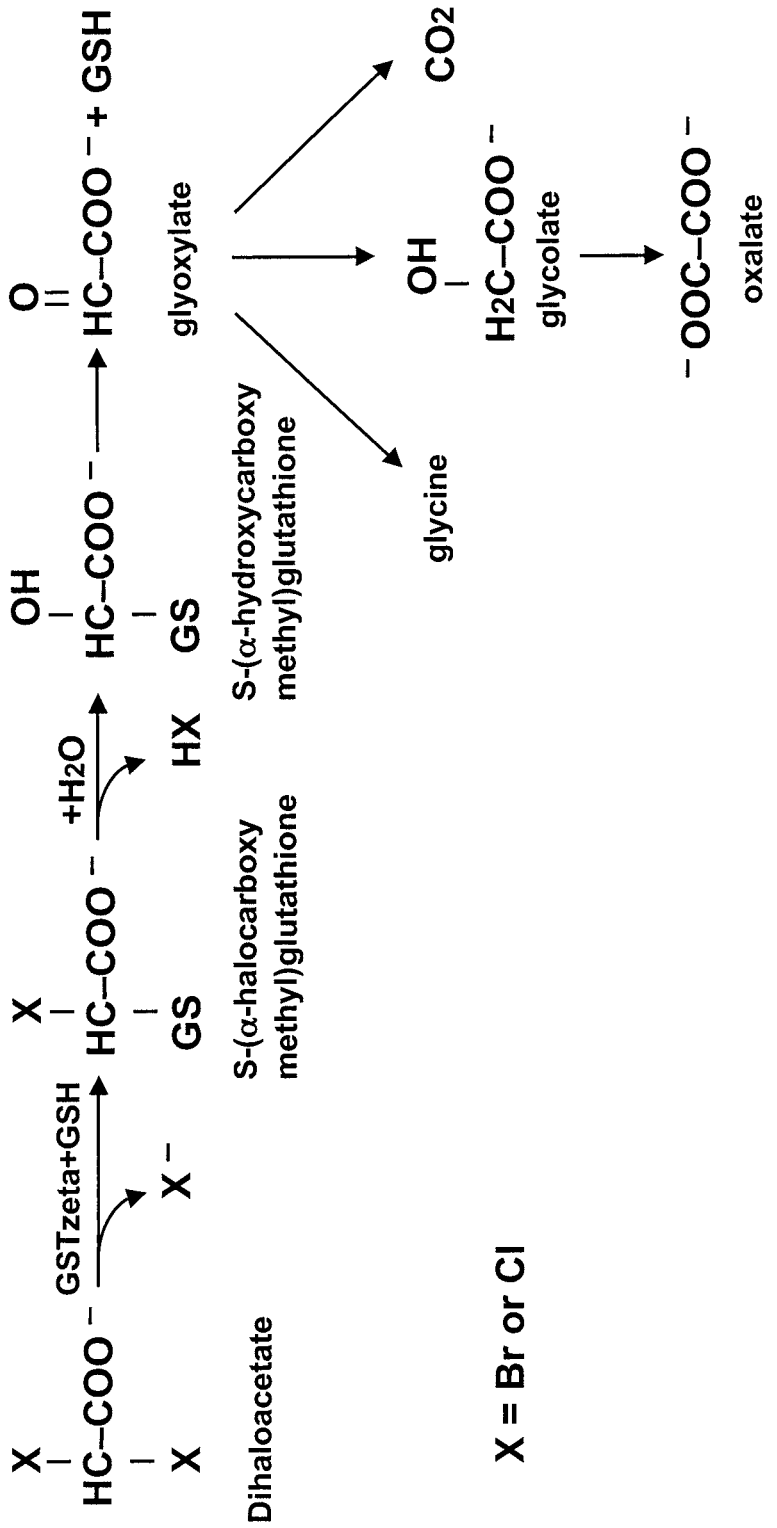


FIGURE 1
Scheme for the Biotransformation of Dihaloacetates (Tong *et al.*, 1998b)

TOXICITY

Experimental Animals

The LD_{50} for dibromoacetate in male Sprague-Dawley rats was reported to be 1,737 mg/kg body weight (Linder *et al.*, 1994a). In male Sprague-Dawley rats gavaged daily with 250 mg dibromoacetate/kg, weight loss was evident by week 3, neurological signs including excitability, awkward gait, atypical limb movement, and abnormal posturing were evident by week 4, and labored breathing, light tremor, and difficulty in moving were observed during week 6 of treatment (Linder *et al.*, 1995).

Studies comparing the effects of dichloroacetate in mouse liver with those of trichloroacetate indicate that these agents likely operate by different mechanisms. Drinking water exposure of male $B6C3F_1$ mice to 2 g dichloroacetate/L for 37 weeks caused hepatomegaly, cytomegaly, focal necrosis, and accumulation of glycogen in hepatocytes; in contrast, exposure of male mice to 2 g trichloroacetate/L drinking water caused marked accumulation of lipofuscin (indicator of lipid peroxidation), modest accumulation of glycogen, and no evidence of focal necrosis (Bull *et al.*, 1990). After 52 weeks of exposure, the incidences of hyperplastic nodules and hepatocellular adenoma and carcinoma were increased in dichloroacetate- and trichloroacetate-exposed mice compared to controls. Similar to dichloroacetate, dibromoacetate and bromochloroacetate caused liver glycogen accumulation in $B6C3F_1$ mice (Kato-Weinstein *et al.*, 2001). In addition, dibromoacetate produced a dose-dependent decrease in serum glucose concentration and transient increases (2 to 4 weeks) in liver cell replication rates and in the activity of the peroxisomal enzyme cyanide-insensitive acyl-CoA oxidase. Dibromoacetate and dichloroacetate induced peroxisomal palmitoyl-CoA oxidase activity in primary rat hepatocyte cultures (Walgren *et al.*, 2004).

In a two-generation drinking water study, absolute and relative liver weights and kidney weights were increased in pups exposed to 50 ppm or greater concentrations of dibromoacetate (Christian *et al.*, 2002). No microscopic changes were associated with these weight increases.

Exposure of adolescent male and female F344/N rats to 0.2 to 1.5 g dibromoacetate/L drinking water for 6 months produced concentration-related neuromuscular toxicity (Moser *et al.*, 2004). Effects of exposure to dibromoacetate included decreased grip strength, mild gait abnormalities, and decreased sensorimotor responsiveness; neuropathological findings included degeneration of spinal cord nerve fibers and spinal cord cellular vacuolization at the 0.6 and 1.5 g/L concentrations. Similar neuromuscular effects had been reported in F344/N rats exposed to dichloroacetate (Moser *et al.*, 1999).

In an evaluation of cytotoxic potency of drinking water disinfection by-products in Chinese hamster ovary cells, dibromoacetate was less potent than bromoacetate and 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone, but more potent than chloroacetate, potassium bromate, tribromoacetate, dichloroacetate, and trichloroacetate (Plewa *et al.*, 2002).

Humans

No studies on the toxicity of dibromoacetate in humans were found in a review of the literature.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Spermatotoxicity in male rats has been identified as one of the most sensitive toxic endpoints following exposure to dibromoacetate and dichloroacetate. In adult male Sprague-Dawley rats administered a single gavage dose of 1,250 mg dibromoacetate/kg body weight, a transient decline in serum testosterone, increases in abnormal sperm head shapes, fusion of spermatid flagella, decreases in epididymal sperm counts, reduction in sperm motility, and delayed spermiation described as abnormal retention of Step 19 spermatids near the lumen of Stage IX to Stage XII tubules were observed (Linder *et al.*, 1994a). In follow-up studies with oral doses of dibromoacetate ranging from 2 to 270 mg/kg for up to 79 days, reduction in epididymal sperm counts and altered spermiation were observed at 10 mg/kg or higher doses (Linder *et al.*, 1994b, 1997a). No abnormalities were detected in the testes or epididymides of rats exposed to 2 mg/kg. In addition, adverse effects on sperm morphology and sperm motility were detected at the 90 mg/kg dose level, and large atypical residual bodies were seen in the lumen and epithelium of seminiferous tubules and in the epididymides. The formation of atypical residual bodies was suggested to be a result of impairment of degradative processes of Sertoli cells. In spite of the changes in sperm quality caused by dibromoacetate, the germinal epithelium appeared intact and

there were no obvious changes in sperm production in exposed rats. Seminiferous tubule atrophy was observed only in the testes of rats dosed with 250 mg dibromoacetate/kg for 42 days and then held without exposure for an additional 186 days (Linder *et al.*, 1997a). The primary spermatotoxic effects of dibromoacetate appear to be delayed spermiation (retention of mature sperm), formation of atypical residual bodies, abnormal sperm morphology, and decreased sperm motility.

Testicular effects caused by dibromoacetate in rats are similar to those of dichloroacetate; however, the potency of dibromoacetate-induced testicular toxicity is greater than that of dichloroacetate (Linder *et al.*, 1997b). Administration of bromochloroacetate to male Sprague-Dawley rats also decreased epididymal sperm counts, decreased the number of motile sperm, increased the number of epididymal sperm with misshapen heads or tail defects, increased the number of atypical residual bodies in seminiferous tubules, and increased the number of Step 19 spermatids retained in Stages X and XI of the spermatogenic cycle (Klinefelter *et al.*, 2002).

Fertility of male Sprague-Dawley rats was not altered by daily gavage treatment with up to 50 mg dibromoacetate/kg body weight for up to 79 days; however, male fertility was compromised in rats treated for 15 days or more with 250 mg/kg (Linder *et al.*, 1995). The latter evaluation was made through natural breeding and after artificial insemination of female rats with sperm collected from exposed rats. The fertility of cauda epididymal sperm was also reduced in male rats exposed to 8 mg bromochloroacetate/kg or greater doses for 14 days (Klinefelter *et al.*, 2002). The latter evaluation was made by *in utero* insemination. In fertility assessments by intrauterine insemination, the ED_{50} for decreased male fertility of cauda epididymal sperm collected from Sprague-Dawley rats exposed by gavage for 14 days to dibromoacetate (3.5 mg/kg, 16.1 µmol/kg) was similar to the ED_{50} for bromochloroacetate (2.7 mg/kg, 15.6 µmol/kg) (Kaydos *et al.*, 2004).

Holtzman rats were administered dibromoacetate by gavage at doses ranging from 62.5 to 250 mg/kg per day during the first 8 days of pregnancy to determine whether exposure to dibromoacetate during early pregnancy affects female reproduction (Cummings and Hedge, 1998). No effects were detected on the number of implantation sites, number of pups per litter, number of resorptions, or pup weights on day 20; however, serum levels of estradiol were elevated in exposed dams. In a follow-up study, gavage dosing of 90-day old female Sprague-Dawley rats with 10 to 270 mg dibromoacetate/kg for 14 days caused a dose-related alteration in estrous cyclicity, with a tendency toward longer periods of persistent estrus (Balchak *et al.*, 2000). In addition, *in vitro* exposure of preovulatory follicles to dibromoacetate (50 µg/mL for 24 hours) caused an elevation in estradiol release and suppression of progesterone secretion stimulated with human chorionic gonadotropin; thus, the disruption of estrous cyclicity by dibromoacetate was attributed to alteration of ovarian steroid production. Elevations in circulating estradiol in female rats exposed to dibromoacetate were attributed to suppression of estradiol catabolism because serum estradiol levels were elevated in ovariectomized rats implanted with estradiol-containing capsules and then treated with dibromoacetate (Goldman and Murr, 2003). Daily exposure of female Dutch-belted rabbits to approximately 1 to 50 mg dibromoacetate/kg body weight per day in drinking water beginning on gestation day 15 and continuing through 24 weeks did not produce any gross abnormalities of the reproductive tract or viscera, but did reduce the number of primordial follicles in prepubertal and adult rabbits (Bodensteiner *et al.*, 2004). This exposure covers the fetal and neonatal periods when the primordial follicle pool in rabbits is formed. Reduction in the population of primordial follicles could result in early reproductive senescence.

Exposure of Sprague-Dawley rats to 4 to 800 ppm dibromoacetate in drinking water from gestation day 15 through adulthood induced delays in pubertal development (delayed preputial separation in males and delayed vaginal opening in females at 400 ppm), and decreases in the fertility of cauda epididymal sperm at 600 and 800 ppm (Klinefelter *et al.*, 2004). The incidences of atypical residual bodies, delayed spermiation, misshapen sperm heads, and atrophic seminiferous tubules were increased at 400 ppm and greater concentrations; sperm motility and fertility were decreased at 600 and 800 ppm. Altered steroidogenesis was suggested to be a contributor to the pubertal delays.

Dibromoacetate was administered to Sprague-Dawley rats in drinking water at concentrations ranging from 125 to 1,000 ppm (mg/L) with exposures beginning 14 days before cohabitation and continuing through gestation and lactation (Christian *et al.*, 2001). The only reported reproductive and developmental effects were reductions in mating performance at 1,000 ppm and decreases in pup body weights at 250 ppm and greater levels.

In a two-generation reproductive toxicity study, Sprague-Dawley rats were given dibromoacetate in drinking water at concentrations of 0, 250, 500, or 650 ppm (Christian *et al.*, 2002). No effects on estrous cyclicity, mating, fertility, implantation sites, litter sizes, pup viability, or pup sex ratios were observed in the parental or F_1 generation female rats. In parental and F_1 generation male rats, increased incidences of delayed sperm production (retention of Step 19 spermatids in Stage IX and Stage X seminiferous tubules), atypical residual bodies in the testis, abnormal sperm shape, and epididymal abnormalities (atrophy, residual bodies, and hypospermia) were observed in the 250 ppm or 650 ppm exposure groups. Delays in preputial separation and vaginal opening were observed in 650 ppm groups of F_1 generation rats. In contrast to the effect of dibromoacetate on follicular development in rabbits (Bodensteiner *et al.*, 2004), no effect on ovarian follicular histology was observed in rats exposed to dibromoacetate. For this effect, the rabbit may be a more sensitive species.

Twenty-four hour exposures of mouse embryo cultures to haloacetates produced adverse effects on neural tube closure, craniofacial development, and heart development (Hunter *et al.*, 1996). For induction of neural tube defects, dibromoacetate was more potent than dichloroacetate.

Humans

No human studies have been reported on reproductive or developmental effects of dibromoacetate *per se*; however, several studies have indicated an association between exposure to disinfection by-products and alterations in reproductive function or fetal development, including spontaneous abortions, stillbirths, low birth weight, and birth defects (Nieuwenhuijsen *et al.*, 2000).

CARCINOGENICITY

Experimental Animals

No studies have been reported on the carcinogenicity of dibromoacetate in animals. In contrast, several studies have shown that dichloroacetate administered in drinking water is carcinogenic to the liver of rats and mice. Hepatocellular adenomas and carcinomas were induced in male B6C3F_1 mice exposed to 5 g dichloroacetate/L drinking water for 61 weeks (Herren-Freund *et al.*, 1987). The same dose of trichloroacetate was also carcinogenic to male mice; however, the incidences of hepatocellular adenoma and carcinoma in mice exposed to trichloroacetate (8 of 22 or 7 of 22, respectively) were less than those induced with dichloroacetate (25 of 26 or 21 of 26, respectively). In a follow-up drinking water study, the incidences of liver tumors in male B6C3F_1 mice administered 0, 0.05, 0.5, 3.5, or 5 g dichloroacetate/L for 60 weeks were 7%, 24%, 11%, 100%, and 90%, respectively, and the mean daily doses of dichloroacetate in the exposed groups were estimated to be 7.6, 77, 410, and 486 mg dichloroacetate/kg body weight, respectively (DeAngelo *et al.*, 1991). Liver tumor incidences in the 0.05 and 0.5 g/L groups were not significantly different from controls. However, when male B6C3F_1 mice were exposed to 0.5 g dichloroacetate/L drinking water for 104 weeks (mean daily dose, 93 mg/kg), the incidences of hepatocellular carcinoma and adenoma were 63% and 42%, respectively, in animals that survived to the end of the study; the combined incidences of liver tumors were 3/20 in controls and 18/24 in dichloroacetate-exposed mice (Daniel *et al.*, 1992).

Hepatocellular adenomas and carcinomas were induced in female B6C3F_1 mice exposed to 20 mmol dichloroacetate/L drinking water (2.6 g/L) for 576 days (82 weeks), and hepatocellular adenomas were induced in female mice exposed to 6.67 mmol dichloroacetate/L (0.83 g/L). Hepatocellular adenomas and carcinomas were also induced in female B6C3F_1 mice exposed to 20 mmol trichloroacetate/L drinking water (3.3 g/L) for 576 days, and hepatocellular carcinomas were induced in female mice exposed to 6.7 mmol trichloroacetate/L (1.1 g/L) (Pereira, 1996). Dichloroacetate induced a predominance of eosinophilic hepatic foci and tumors, which consistently stained for the presence of glutathione-*S*-transferase (GST-π); in contrast, tumors induced by trichloroacetate were predominantly basophilic and lacked GST-π. In addition, hepatocyte proliferation was increased after 5 days of exposure to dichloroacetate or trichloroacetate, but not after 12 or 33 days of exposure.

Based on an analyses of the time- and dose-dependent relationships for the effects of dichloroacetate on the induction of preneoplastic and neoplastic lesions in the livers of exposed mice (DeAngelo *et al.*, 1999), it was suggested that dichloroacetate-induced hepatocarcinogenesis is due to selective growth of a phenotypic cell-type (basophilic and/or clear cell focal lesions) that does not respond to normal homeostatic control mechanisms, such as cells that are resistant to mitoinhibition (Carter *et al.*, 2003). Hepatocellular necrosis and regenerative

hyperplasia, as well as steatosis, were not associated with the development of tumors or preneoplastic lesions.

Dichloroacetate is also carcinogenic to the liver of rats. Male F344/N rats were exposed to 0, 0.05, 0.5, or 1.6 g dichloroacetate/L drinking water for 100 weeks (DeAngelo *et al.*, 1996). Mean daily doses of dichloroacetate were 3.6, 40, and 139 mg/kg body weight for the three exposed groups. The incidences of hepatocellular adenoma or carcinoma combined in rats that survived more than 78 weeks were 3% (1/33) in controls and 0% (0/26), 24.1% (7/29), and 28.6% (8/28) in the respective exposed groups. The liver cancer response was not associated with peroxisome proliferation, hepatocellular necrosis, or sustained hepatocyte proliferation.

Several studies have examined potential mechanisms of hepatocarcinogenesis of dihaloacetates. Single gavage administration of halogenated acetic acids induced lipid peroxidation and formation of 8-hydroxydeoxyguanosine adducts in nuclear DNA in the liver of male $B6C3F_1$ mice; the relative potencies for these effects were dibromoacetate ≈ bromochloroacetate > dichloroacetate > trichloroacetate (Austin *et al.*, 1996). These results suggest that DNA damage from oxidative stress induced by these agents may contribute to the hepatocarcinogenic process. In male $B6C3F_1$ mice exposed to 2.0 g dichloroacetate/L drinking water, hepatocyte division rates were increased after 14 days of exposure; after 28 or 280 days of exposure, hepatocyte division rates were reduced in livers of dichloroacetate-treated mice compared to controls (Stauber and Bull, 1997). Altered hepatic foci and liver tumors in dichloroacetate-treated mice showed higher immunoreactivity to the oncoproteins c-*Jun* and c-*Fos* and higher rates of cell division than the surrounding nonlesioned liver tissue. Increased cell replication rates in hepatic foci and tumors and decreased rates in normal hepatocytes of mice exposed to dichloroacetate provide a selective growth advantage to initiated cells. In a follow-up study, incubation of primary hepatocyte cultures from untreated male $B6C3F_1$ mice with 0.5 to 2.0 mM dichloroacetate enhanced the formation of anchorage-independent colonies in soft agar (Stauber *et al.*, 1998). A fourfold increase in colony formation was measured when hepatocytes were obtained from mice pretreated with 0.5 g dichloroacetate/L drinking water for 2 weeks. Although dichloroacetate did not induce c-*Jun* expression in hepatocyte monolayers, the colonies promoted by dichloroacetate were immunoreactive with c-*Jun* antibody. These results suggest that dichloroacetate was selective for c-Jun^+ subpopulations.

Gavage administration of 500 mg dichloroacetate/kg body weight to female $B6C3F_1$ mice for 5 days caused decreased DNA methylation and increased mRNA expression of the c-*myc* proto-oncogene (Pereira *et al.*, 2001). Administration of 3.2 g dichloroacetate/L drinking water for 36 weeks increased the incidence and multiplicity of liver tumors but not kidney tumors in *N*-methyl-*N*-nitrosourea-initiated mice. Thus, hypomethylation of c-*myc* and increased expression of this gene may be involved in the promotion of liver tumors by dichloroacetate. Exposure of female $B6C3F_1$ mice and male F344/N rats to 1,000 or 2,000 mg dibromoacetate/L drinking water for 28 days caused a decrease in the 5-methylcytosine content of DNA and hypomethylation and increased mRNA expression of the c-*myc* and insulin-like growth factor II genes (Tao *et al.*, 2004). Treatment with dibromoacetate also caused glycogen accumulation and peroxisome proliferation in the mouse and rat liver. Thus, dibromoacetate and dichloroacetate induce similar biochemical and molecular effects, some of which may be involved in hepatocarcinogenesis.

The mutational spectrum at codon 61 of the H-*ras* gene was different in liver tumors obtained from male $B6C3F_1$ mice exposed to 500 mg dichloroacetate/L drinking water for 76 weeks compared to liver tumors from control mice (Anna *et al.*, 1994). Although the frequency of liver tumors with H-*ras* codon 61 mutations was not significantly different in dichloroacetate-exposed (62%) and control (69%) mice, the dichloroacetate-treated mice had increased CAA→CTA and decreased CAA→AAA mutations. Hence, base-substitution mutations may be involved in the hepatocarcinogenicity of dichloroacetic acid.

Humans

No studies have been reported on the carcinogenicity of dibromoacetate in humans *per se*; however, several studies have examined cancer risks associated with exposure to disinfection by-products. A meta-analysis of epidemiology studies published before 1989 on cancer and chlorination by-products in drinking water yielded a relative risk estimate of 1.21 [95% confidence interval (CI): 1.09 to 1.34] for bladder cancer and 1.38 (95% CI: 1.01 to 1.87) for rectal cancer (Morris *et al.*, 1992). A population-based case-control study in Colorado also

found an association between prolonged exposures to chlorinated surface water and increased bladder cancer risk in men and women for both smokers and nonsmokers (McGeehin *et al.*, 1993). An elevation in brain cancer risk was also associated with exposure to chlorinated surface water (Cantor *et al.*, 1999).

Dichloroacetate is listed as likely to be carcinogenic in humans by the United States Environmental Protection Agency (USEPA, 2003). Based on sufficient evidence of carcinogenicity in experimental animals, dichloroacetate was listed by the International Agency for Research on Cancer (IARC, 2004) as possibly carcinogenic to humans (Group 2B).

Genetic Toxicity

Several studies have demonstrated genotoxicity of dihaloacetates. Both dibromoacetate and dichloroacetate induced DNA damage in the *Escherichia coli* SOS repair assay, and both were mutagenic in *Salmonella typhimurium* strain TA100 in an Ames fluctuation test (Giller *et al.*, 1997). Dibromoacetate and dichloroacetate were also reported to be mutagenic in *S. typhimurium* strains TA98 and TA100 with and without metabolic activation (Kargalioglu *et al.*, 2002); however, dibromoacetate was the more potent mutagen in these two strains. In strain RSJ100, a derivative of TA1535 containing a rat GSTT1-1 gene, dichloroacetate was mutagenic, but dibromoacetate was not. Dibromoacetate also induced DNA strand breaks in Chinese hamster ovary cells as measured by the Comet assay (Plewa *et al.*, 2002); dichloroacetate was not genotoxic in this assay. Administration of dibromoacetate or bromochloroacetate in drinking water to male B6C3F_1 mice at concentrations of 0.1, 0.5, or 2.0 g/L for 3 weeks produced increases in the content of 8-hydroxydeoxyguanosine in liver nuclear DNA; this effect, indicative of oxidative DNA damage, was not seen after administration of dichloroacetate (Parrish *et al.*, 1996). A metabolite of dihaloacetate biotransformation, glyoxylate, is mutagenic in *S. typhimurium* strains TA97, TA100, and TA104 in the absence of S9; glyoxylate was mutagenic in strain TA102 in the presence of S9 (Sayato *et al.*, 1987).

Dichloroacetate induced prophage lambda in *E. coli* and mutations in *S. typhimurium* strain TA100 that were primarily GC→AT transitions (DeMarini *et al.*, 1994). An increase in mutant frequency was observed in the liver of transgenic male B6C3F_1 mice (harboring the bacterial *lacI* gene) that were exposed to 1.0 or 3.5 g dichloroacetate/L drinking water for 60 weeks (Leavitt *et al.*, 1997); mutations were primarily GC→AT transitions, as well as transitions and transversions at TA sites. In addition, dichloroacetate induced gene mutations and chromosome aberrations in L5178Y/$TK^{+/-}$ mouse lymphoma cells (Harrington-Brock *et al.*, 1998). Male B6C3F_1 mice were exposed to dichloroacetate in drinking water at concentrations of 0.5, 1, 2, or 3.5 g/L for up to 31 weeks and evaluated for genotoxic effects in peripheral blood (Fuscoe *et al.*, 1996). Small but significant increases were observed in the frequencies of polychromatic and normochromatic erythrocytes; in addition, the authors suggested that dichloroacetate may also cause DNA crosslinking because DNA migration from leukocytes of exposed mice was decreased in the Comet assay. In contrast to many of the above studies that indicate genotoxic activity of dichloroacetate, Fox *et al.* (1996) reported that sodium dichloroacetate did not induce mutations in *Salmonella*, *E. coli*, or L5178Y mouse lymphoma cells, did not induce chromosomal aberrations in Chinese hamster ovary cells, and did not induce micronuclei in rat bone marrow cells.

Study Rationale

Dibromoacetic acid was nominated to the NTP by the United States Environmental Protection Agency for toxicity and carcinogenicity studies in rats and mice because of widespread human exposure to this brominated water disinfection by-product and because a related dihaloacetate, dichloroacetate, was found to be carcinogenic to the liver of rats and mice. Drinking water was selected as the route of exposure to mimic human exposure to this chemical.

MATERIALS AND METHODS

Procurement and Characterization of Dibromoacetic Acid

Dibromoacetic acid was obtained from Fluka (Buchs, Switzerland) in one lot (46019/1 55196). Lot 46019/1 55196 was used in the 2-week, 3-month and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory at Battelle Columbus Operations (Columbus, OH) and by the study laboratory at Southern Research Institute (Birmingham, AL) (Appendix I). Karl Fischer titration, elemental analysis, and melting point determination were performed by Galbraith Laboratories, Inc. (Knoxville, TN).

Lot 46019/1 55196, a clumped white powder or moist white crystalline solid, was identified as dibromoacetic acid by the study laboratory using infrared spectroscopy and by the analytical chemistry laboratory using infrared, ultraviolet/visible, and proton and carbon-13 nuclear magnetic resonance spectroscopy. The purity of lot 46019/1 55196 was determined by the analytical laboratory using functional group titration, ion chromatography, and high performance liquid chromatography (HPLC) and by the study laboratory using HPLC.

Karl Fischer titration indicated 0.27% water. Elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values for dibromoacetic acid. The melting point determination was slightly higher (38.6° C) than that given by the manufacturer's certificate of analysis and Material Safety Data Sheet (32° to 38° C). Functional group titration indicated a purity of greater than 100% which was consistent with the manufacturer's certificate of analysis. Ion chromatography (IC) indicated one major peak and two impurities with a combined area of 3.4% (3.2% and 0.2%). Using HPLC and standard addition, the 3.2% impurity seen by IC was found to have the same retention time as monobromoacetic acid and was shown to be overestimated by IC. HPLC, with standard addition, indicated one major peak and one impurity with a relative peak area of 0.34%. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using HPLC. These studies indicated that dibromoacetic acid showed no degradation after 15 days when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in sealed amber glass containers.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared once during the 2-week studies, four times during the 3-month studies, and approximately every 2 weeks throughout the 2-year studies. The dose formulations were prepared by mixing dibromoacetic acid with tap water. Formulations were adjusted to pH 5 with 0.1 N sodium hydroxide and stored in sealed opaque glass or Nalgene® containers at 5° C for up to 42 days.

Homogeneity studies of 125 and 2,000 mg/mL formulations were conducted by the study laboratory, and stability studies of a 10 µg/mL formulation (pH 5) were conducted by the analytical study laboratory using IC. Homogeneity was confirmed, and stability was confirmed for up to 42 days when stored at 5° C in sealed opaque glass or Nalgene® containers and at animal room conditions for up to 3 days.

Periodic analyses of the dose formulations of dibromoacetic acid were conducted by the study laboratory using IC. During the 2-week studies, the dose formulations were analyzed once; all five of the dose formulations for rats and mice were within 10% of the target concentrations, with no value greater than 10% of the target concentration. Animal room samples of these dose formulations were also analyzed; all 23 samples analyzed were within 10% of the target concentrations. During the 3-month studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies; all 20 of the dose formulations used for rats and mice were within 10% of the target concentrations, with no value more than 9% from the target concentration. Animal room samples of these dose formulations were also analyzed; 26 of 30 samples were within 10% of the

target concentrations. During the 2-year studies, the dose formulations were analyzed approximately every 7 to 8 weeks. All 34 of the dose formulations analyzed were within 10% of the target concentrations. Animal room samples of these dose formulations were also analyzed; 23 of 24 samples were within 10% of the target concentrations.

2-Week Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms, Inc. (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 12 (mice) or 13 (rats) days and were 6 weeks old on the first day of the studies. Groups of five male and five female rats and mice were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg dibromoacetic acid/L in the drinking water for 15 days. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage, and male mice were house individually. Clinical findings were recorded daily for rats and mice. Water consumption was recorded weekly for a 7-day period. The animals were weighed initially, on day 8, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Necropsies were performed on all animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on the kidney, liver, lung, and testis of 0 and 2,000 mg/L rats and mice; these tissues were examined to a no-effect level in the remaining exposure groups.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to dibromoacetic acid and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms, Inc. (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Rats were quarantined for 11 (males) or 12 (females) days, and mice were quarantined for 13 (females) or 14 (males) days; rats and mice were 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were exposed to 0, 125, 250, 500, 1,000, or 2,000 mg dibromoacetic acid/L in the drinking water for 3 months; groups of 10 male and 10 female special study rats and mice were exposed to the same concentrations for 4 weeks. Feed and water were available *ad libitum*. Rats and female mice were housed five per cage, and male mice were housed individually. Clinical findings were recorded weekly for core study rats and mice. Water consumption was measured weekly for a 7-day period. The animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected from the retroorbital sinus of special study rats on days 4 and 21 and from core study rats and mice at the end of the studies for hematology (rats and mice) and clinical chemistry (rats) analyses. Animals were anesthetized with a CO_2/O_2 mixture. The parameters measured are listed in Table 1. Blood samples for hematology were placed in tubes containing EDTA. Erythrocyte, platelet, and leukocyte counts; hematocrit value; hemoglobin concentration; and mean cell volume, hemoglobin, and hemoglobin concentration were determined using a Technicon H-1™ (Bayer HealthCare LLC, Tarrytown, NY) with reagents from Bayer, Inc. (Tustin, CA), R&D Systems, Inc. (Minneapolis, MN), or Fisher Scientific (Norcross, GA). Reticulocytes were counted using a Coulter Model Elite XL Flow Cytometer (Coulter Corp., Miami, FL) with reagents supplied by the manufacturer or Molecular Probes (Eugene, OR). Samples for clinical chemistry analyses were placed in tubes with no anticoagulent. Samples were analyzed using a Hitachi 911 automated analyzer (Roche Diagnostics Corporation, Indianapolis, IN) with reagents from Boehringer Mannheim Biochemicals (Indianapolis, IN) or Sigma Chemical Co. (St. Louis, MO), except sorbitol dehydrogenase was measured using a Cobas Fara chemistry analyzer (Roche Diagnostics Corporation).

On day 22 and for 5 days thereafter, 0.4 mg/mL BrdU was added to the drinking water of groups of 10 special study rats and mice. These animals were weighed and then sacrificed by CO_2 asphyxiation on day 27 for cell

proliferation studies. The liver was weighed, and the brain, colon, duodenum, kidney, liver, and urinary bladder were collected and fixed in 10% neutral buffered formalin for 18 to 24 hours, embedded in paraffin, and shipped to NTP. The duodenum and liver from 0, 500, 1,000, and 2,000 mg/L rats and mice were shipped to Pathology Associates Division of Charles River Laboratories (Frederick, MD) for analyses of labeled and unlabeled hepatocytes to determine the BrdU labeling index. Tissue sections were incubated with a monoclonal antibody to BrdU (Becton Dickenson 1:100 for rats and Serotec 1:100 for mice) and reagents required for the avidin-biotin peroxidase (Vectasin ABC peroxidase kit, Vector Laboratories, Burlingame, CA) method for the detection of the antigen-antibody complex. BrdU incorporated into cells in S phase was localized by the chromagen 3,3′-diaminobenzidine tetrahydrochloride, and tissues were counterstained with hematoxylin. The percentage of nuclear-stained hepatocytes was scored in at least 3,000 hepatocytes in 10 fields per slide at 200×.

At the end of the 3-month studies, samples were collected for sperm count and motility and vaginal cytology evaluations on 10 male and 10 female core study rats and mice exposed to 0, 500, 1,000, or 2,000 mg/L. The parameters evaluated are listed in Table 1. For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Necropsies were performed on all core study rats and mice. The heart, right kidney, liver, lung, right testis, and thymus of core study animals were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on 0 and 2,000 mg/L rats and mice. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were exposed to 0, 50, 500, or 1,000 mg dibromoacetic acid/L in the drinking water for 105 to 106 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms, Inc. (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 14 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Male rats were housed up to three per cage, and female rats and mice were housed five per cage; male mice were housed individually. Feed and water were available *ad libitum*. During the course of these studies, tap water samples at the study laboratory were found to contain 44.7 ± 22.6 µg/L of dihaloacetic acids and 3.8 ± 2.9 µg/L of dibromoacetic acid. Cages and racks were rotated twice weekly. Further details of animal maintenance are given in Table 1. Information on feed

composition and contaminants is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded at 4-week intervals beginning at week 5. Water consumption was recorded weekly for the first 13 weeks, then for 7 days every 4 weeks. Body weights were recorded on day 1, weekly during the first 13 weeks, at 4-week intervals thereafter, and at terminal sacrifice.

Complete necropsies and microscopic examinations were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the liver and lung of male and female rats and mice; the epididymis, kidney, mediastinal lymph node, mesentery, peritoneum, seminal vesicle, spleen, and testis of male rats; the kidney, pancreatic islets, spleen, uterus, and vagina of female rats; the bone marrow, eye, harderian gland, kidney, mandibular lymph node, pancreatic islets, and parathyroid gland of male mice; and the mesenteric lymph node, pancreatic islets, spleen, and thymus of female mice.

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

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Dibromoacetic Acid

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species		
F344/N rats B6C3F$_1$ mice	F344/N rats B6C3F$_1$ mice	F344/N rats B6C3F$_1$ mice
Animal Source		
Taconic Farms, Inc. (Germantown, NY)	Taconic Farms, Inc. (Germantown, NY)	Taconic Farms, Inc. (Germantown, NY)
Time Held Before Studies		
Rats: 13 days Mice: 12 days	Rats: 11 (males) or 12 (females) days Mice: 14 (males) or 13 (females) days	14 days
Average Age When Studies Began		
6 weeks	6 weeks	6 weeks
Date of First Exposure		
Rats: November 25, 1998 Mice: November 24, 1998	Rats: February 15 (males) or 16 (females), 1999 Mice: February 17 (females) or 18 (males), 1999	Rats: March 8, 2000 Mice: February 23, 2000
Duration of Exposure		
15 days	14 weeks	105 to 106 weeks
Date of Last Exposure		
Rats: December 9, 1998 Mice: December 8, 1999	Rats: May 17 (males) or 18 (females), 1999 Mice: May 19 (females) or 20 (males), 1999	Rats: March 14, 2002 Mice: February 28, 2002
Necropsy Dates		
Rats: December 9, 1998 Mice: December 8, 1998	Rats: May 17 (males) or 18 (females), 1999 Mice: May 19 (females) or 20 (males), 1999	Rats: March 6-14, 2002 Mice: February 20-28, 2002
Average Age at Necropsy		
8 weeks	19 weeks	110 to 111 weeks
Size of Study Groups		
5 males and 5 females	Core: 10 males and 10 females Special Study: 10 males and 10 females	50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 2-week studies	Same as 2-week studies
Animals per Cage		
Rats: 5 Mice: 1 (males); 5 (females)	Rats: 5 Mice: 1 (males); 5 (females)	Rats: 3 (males); 5 (females) Mice: 1 (males); 5 (females)
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Dibromoacetic Acid

2-Week Studies	3-Month Studies	2-Year Studies
Diet Irradiated NTP-2000 wafer rodent feed (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Irradiated NTP-2000 pelleted rodent feed (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 2-week studies
Water Tap water (Birmingham, AL, municipal water supply) provided in amber glass bottles (Wheaton, Millville, NJ) with Teflon®-lined caps and stainless steel sipper tubes (Allentown Caging, Allentown, NJ), available *ad libitum*, changed twice weekly	Same as 2-week studies	Same as 2-week studies
Cages Solid bottom polycarbonate (Lab Products, Inc., Maywood, NJ) changed once (male mice) or twice weekly	Same as 2-week studies	Same as 2-week studies
Bedding Heat-treated irradiated hardwood chips (P.J. Murphy Forest Products, Corp., Montville, NJ); changed with cage once (male mice) or twice weekly	Same as 2-week studies	Same as 2-week studies
Cage Filters Reemay® spun-bonded polyester (Andico, Birmingham, AL) changed every 2 weeks	Same as 2-week studies	Same as 2-week studies
Racks Stainless steel (Lab Products, Inc., Maywood, NJ) changed every 2 weeks	Same as 2-week studies	Same as 2-week studies
Animal Room Environment Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations 0, 125, 250, 500, 1,000, or 2,000 mg/L in drinking water	0, 125, 250, 500, 1,000, or 2,000 mg/L in drinking water	0, 50, 500, or 1,000 mg/L in drinking water
Type and Frequency of Observation Observed twice daily; animals were weighed initially, on day 8, and at the end of the studies; clinical findings were recorded daily. Water consumption was recorded weekly.	Observed twice daily; core study animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly. Water consumption was recorded weekly.	Observed twice daily; animals were weighed initially, weekly for the first 13 weeks, at 4-week intervals thereafter, and at the end of the studies; clinical findings were recorded at 4-week intervals beginning at week 5. Water consumption was recorded weekly for the first 13 weeks, and every 4 weeks thereafter.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Dibromoacetic Acid

2-Week Studies	3-Month Studies	2-Year Studies
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsies were performed on all animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all animals.
Clinical Pathology None	Blood was collected from the retroorbital sinus of special study rats on days 4 and 21 and from core study rats and mice at the end of the studies for hematology (rats and mice) and clinical chemistry (rats). ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticuloctye, and platelet counts; erythrocyte morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids	None
Histopathology Microscopic examinations were performed on 0 and 2,000 mg/L animals. In addition to gross lesions and tissue masses, the following tissues were examined to a no-effect level: kidney, liver, lung, testis, and thymus.	Complete histopathologic examinations were performed on core study animals exposed to 0 or 2,000 mg/L. In addition to gross lesions and tissue masses, the following tissues were examined to a no-effect level: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis with epididymis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eye, gallbladder (mice), harderian gland, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spleen, stomach (forestomach and glandular), testis with epididymis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Dibromoacetic Acid

2-Week Studies	3-Month Studies	2-Year Studies
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from core study male animals in the 0, 500, 1,000, and 2,000 mg/L groups for sperm count and motility evaluations. The following parameters were evaluated: spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from core study female animals in the 0, 500, 1,000, and 2,000 mg/L groups for vaginal cytology evaluations. The estrous cycle length was evaluated.	None
Cell Proliferation		
None	From days 22 to 27, BrdU was added to the drinking water of special study rats and mice. On day 27, the livers of these animals were weighed, and the brain, colon, duodenum, kidney, liver, and urinary bladder were collected and fixed. The duodenum and liver of 0, 500, 1,000, and 2,000 mg/L rats and mice were evaluated for BrdU-labeled and unlabeled cells.	None

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344/N rats and B6C3F_1 mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) (as modified by Williams, 1986) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons

than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1957) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations. The BrdU labeling index was analyzed for significance using the Student's *t*-test (two sided, unequal variance).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The current NTP historical database contains all studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison, including the present study.

Quality Assurance Methods

The 3-month and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of dibromoacetic acid was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and increases in the frequency of micronucleated erythrocytes in peripheral blood of exposed mice. Micronuclei (literally "small nuclei" or Howell-Jolly bodies) are biomarkers of induced structural or numerical chormosomal alterations and are formed when acentric fragments or whole chomosomes fail to incorporate into either of two daughter nuclei during cell division (Schmid, 1975; Heddle *et al.*, 1983). The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However,

these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-WEEK STUDY

All rats survived to the end of the study (Table 2). Final mean body weights of male and female rats were similar to those of the controls; mean body weight gains of 1,000 mg/L males and of 500 mg/L females were significantly greater than those of the controls. Water consumption by exposed and control groups was similar. Drinking water concentrations of 125, 250, 500, 1,000, and 2,000 mg/L resulted in average daily doses of approximately 17, 31, 67, 134, and 270 mg dibromoacetic acid/kg body weight to males and 17, 33, 67, 135, and 257 mg/kg body weight to females. There were no clinical findings related to dibromoacetic acid exposure.

Liver weights of all exposed groups of males and females were significantly increased (Table G1). Absolute and relative heart weights of male rats in the 2,000 mg/L group and relative heart weights of all other groups of males and females exposed to 500 mg/L or greater were significantly less than those of the controls. Right testis weights of males exposed to 500 mg/L or greater were significantly decreased.

TABLE 2
Survival, Body Weights, and Water Consumption of Rats in the 2-Week Drinking Water Study of Dibromoacetic Acid

Concentration (mg/L)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	102 ± 3	161 ± 4	58 ± 2		14.5	14.8
125	5/5	101 ± 4	169 ± 6	68 ± 3	105	15.4	15.4
250	5/5	104 ± 4	167 ± 8	62 ± 4	104	14.3	14.5
500	5/5	100 ± 3	167 ± 5	67 ± 2	104	15.2	15.1
1,000	5/5	102 ± 4	171 ± 4	69 ± 3*	106	15.6	15.3
2,000	5/5	101 ± 3	166 ± 5	65 ± 3	103	15.2	15.6
Female							
0	5/5	90 ± 3	120 ± 3	30 ± 2		12.1	11.8
125	5/5	86 ± 1	121 ± 2	35 ± 3	101	12.9	12.2
250	5/5	93 ± 2	129 ± 2	36 ± 1	107	13.6	12.7
500	5/5	87 ± 3	125 ± 3	38 ± 1*	104	13.5	12.3
1,000	5/5	84 ± 2	118 ± 4	34 ± 2	98	13.0	11.8
2,000	5/5	89 ± 3	124 ± 4	35 ± 1	103	12.8	12.0

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Water consumption is expressed as grams per animal per day.

Histopathologically, testicular lesions were noted in males exposed to 500 mg/L or higher concentrations. The lesions were characterized by delays in spermiation. Step 19 spermatids were retained and found in the outermost part of seminiferous epithelium adjacent to the lumen in stages IX and X of the spermatogenic cycle. These changes were occasionally accompanied by large residual bodies. The overall severity of the lesions was mild. In the 1,000 mg/L group, all five animals had delayed spermiation with retained spermatids. In the 500 mg/L group, four animals had delayed spermiation with retained spermatids, and a single animal was without abnormalities. No abnormalities were observed in the 250 mg/L group.

The incidences of minimal, diffuse hepatocytic cytoplasmic alteration were significantly increased in males exposed to 500 mg/L or greater and in 2,000 mg/L females (males: 0 mg/L, 0/5; 125 mg/L, 0/5; 250 mg/L, 2/5; 500 mg/L, 5/5; 1,000 mg/L, 5/5; 2,000 mg/L, 5/5; females: 0 mg/L, 0/5; 1,000 mg/L, 0/5; 2,000 mg/L, 5/5). Affected hepatocytes were considered minimally enlarged, granular or vacuolated (up to 25% greater than normal). The hepatocellular change caused the appearance of tightly packed cells with resulting compression of sinusoids. The cytoplasm of affected cells appeared pale and stained lightly eosinophilic. The hepatocellular cytoplasm in control rats was characterized by a more homogenous and darker eosinophilic staining appearance.

Exposure Concentration Selection Rationale: Based on the lack of lethality, clinical signs of toxicity, water consumption changes, and body weight changes, dibromoacetic acid exposure concentrations selected for the 3-month drinking water study in rats were 125, 250, 500, 1,000, and 2,000 mg/L. The 2,000 mg/L concentration provides a dose of dibromoacetic acid that has been reported to cause decreases in body weight gain and neurologic effects in rats with exposures longer than 2 weeks.

3-Month Study

All rats survived to the end of the study (Table 3). Final mean body weights and body weight gains of male and female rats receiving 2,000 mg/L were significantly less than those of the controls. Water consumption by 2,000 mg/L males and females was less than that by controls at weeks 1 and 13. Water consumption by all exposed groups of females at week 13 was generally less than that by controls. Drinking water concentrations of 125, 250, 500, 1,000, and 2,000 mg/L resulted in average daily doses of approximately 10, 20, 40, 90, and 166 mg dibromoacetic acid/kg body weight to males and 12, 23, 48, 93, and 181 mg/kg to females. There were no clinical findings related to dibromoacetic acid exposure.

Liver weights of all exposed groups of males and females were significantly increased (Table G2). Kidney weights of males and females exposed to 500 mg/L or greater were significantly increased. Heart weights of male and female rats in the 2,000 mg/L groups were decreased. Male rats in the 2,000 mg/L group had significantly decreased testis weights. Lung weights were decreased in the 2,000 mg/L females, and thymus weights were decreased in 2,000 mg/L males and in 1,000 and 2,000 mg/L females.

Table 3
Survival, Body Weights, and Water Consumption of Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

Concentration (mg/L)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	82 ± 1	327 ± 5	245 ± 4		14.1	16.4
125	10/10	80 ± 1	334 ± 6	253 ± 6	102	14.1	15.3
250	10/10	82 ± 2	335 ± 4	253 ± 4	103	14.7	16.1
500	10/10	82 ± 1	334 ± 4	253 ± 4	102	15.1	16.5
1,000	10/10	83 ± 1	334 ± 6	251 ± 6	102	16.5	16.5
2,000	10/10	81 ± 2	298 ± 3**	217 ± 3**	91	13.1	15.7
Female							
0	10/10	78 ± 1	192 ± 3	114 ± 2		13.5	13.2
125	10/10	79 ± 2	190 ± 3	111 ± 2	99	13.3	12.7
250	10/10	77 ± 1	190 ± 2	113 ± 2	99	12.8	11.9
500	10/10	76 ± 2	190 ± 3	114 ± 4	99	14.3	12.5
1,000	10/10	76 ± 1	188 ± 3	111 ± 3	98	14.2	11.6
2,000	10/10	77 ± 1	169 ± 2**	92 ± 2**	88	12.6	11.4

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Water consumption is expressed as grams per animal per day.

Hematology and clinical chemistry data are listed in Tables 4 and F1. There were changes in the erythron that would be consistent with a very minimal ineffective erythropoietic response in male and female rats. The erythron alterations were generally characterized by decreases in hematocrit, hemoglobin, mean cell volume, and mean cell hemoglobin values. These changes were small (~8% or less decrease) and occurred in the 1,000 and 2,000 mg/L male and female groups at multiple time points. In males, these alterations were transient and most consistently occurred in the 2,000 mg/L group on day 21; by week 13, there were no differences in the erythron variables between exposed and control animals. In females, the decreases occurred on day 21 and, though ameliorated, were also present at week 14. There were no changes in red blood cell counts, suggesting the treatment effect resulted in a minimal decrease in erythrocyte size only; it was not deemed clinically significant.

In the 2,000 mg/L male and female rats, a small decrease in platelet counts (~15% or less decrease) occurred on day 21 (males) and at week 14 (males and females). The resulting platelet counts suggested a small effect on platelet production, release, or peripheral distribution and were not considered clinically significant.

In the female rats, there were changes in the leukon that would generally be consistent with a physiological stress- or steroid-induced response; the changes were characterized by decreases in white blood cell and lymphocyte counts (Table F1). These changes were not dose-related, were mild (~20% decrease), and occurred in the 1,000 and 2,000 mg/L female groups at week 14.

On day 4, there were increases in serum alkaline phosphatase activities and bile acid concentrations in male and female rats. Alkaline phosphatase activity was increased, but not in a dose-related manner in the 500 mg/L or greater males and females; bile acid concentrations were increased in the 1,000 and 2,000 mg/L groups. The increases in these variables were transient, and on day 21, they had either disappeared or reversed. For example, alkaline phosphatase activities were decreased by less than 20% in exposed male and female animals on day 21. The increases observed for alkaline phosphatase activity and bile acid concentration on day 4 were consistent with an acute cholestatic event that was transient and abrogated on day 21; the mechanism for this effect is unknown.

On day 4, there were small decreases (~10% or less) in serum albumin and/or total protein concentration in 2,000 mg/L male and female groups. This was a transient finding, which was replaced by increased albumin and/or total protein concentration values on day 21. By week 14, significantly increased concentrations (at ~15% or less) occurred in all exposed groups of male and female rats. The increased total protein concentration was probably related to the increased albumin concentration, and since there are no known conditions in which increased albumin production occurs, it would be consistent with a physiological dehydration-type response.

On day 21 and at week 14, decreases in alanine aminotransferase activity occurred in exposed male and female animals, which could suggest an altered enzyme metabolism or inhibition. Other scattered changes in the hematological and clinical chemistry variables occurred but were not considered toxicologically relevant.

TABLE 4
Selected Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male						
Hematology						
n						
Day 4	10	10	10	10	10	10
Day 21	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Hematocrit (%)						
Day 4	45.3 ± 0.8	42.5 ± 0.9	44.2 ± 0.7	43.7 ± 0.5	45.1 ± 0.9	45.7 ± 0.6
Day 21	46.2 ± 0.7	45.5 ± 0.6	45.6 ± 0.6	45.3 ± 0.5	45.5 ± 0.6	42.8 ± 0.6**
Week 14	46.8 ± 0.3	45.7 ± 0.5	45.4 ± 0.6	45.3 ± 0.5*	45.5 ± 0.3	45.3 ± 0.3
Hemoglobin (g/dL)						
Day 4	14.7 ± 0.3	13.9 ± 0.3	14.5 ± 0.2	14.3 ± 0.2	14.7 ± 0.3	15.1 ± 0.2
Day 21	15.4 ± 0.2	15.0 ± 0.2	15.2 ± 0.2	15.0 ± 0.2	15.0 ± 0.2	14.2 ± 0.2**
Week 14	15.4 ± 0.1	15.1 ± 0.2	15.0 ± 0.1*	15.1 ± 0.1	15.1 ± 0.1	15.0 ± 0.1
Erythrocytes (10^6/μL)						
Day 4	7.30 ± 0.12	6.90 ± 0.15	7.20 ± 0.11	7.11 ± 0.11	7.49 ± 0.16	7.66 ± 0.12
Day 21	7.65 ± 0.13	7.49 ± 0.11	7.49 ± 0.10	7.42 ± 0.06	7.63 ± 0.10	7.26 ± 0.11
Week 14	9.08 ± 0.08	8.86 ± 0.10	8.78 ± 0.11	8.80 ± 0.09	8.85 ± 0.07	8.89 ± 0.06
Mean cell volume (fL)						
Day 4	62.0 ± 0.3	61.6 ± 0.3	61.5 ± 0.4	61.4 ± 0.2	60.3 ± 0.5*	59.7 ± 0.2**
Day 21	60.5 ± 0.3	60.8 ± 0.5	60.9 ± 0.4	61.1 ± 0.4	59.7 ± 0.3	59.0 ± 0.3*
Week 14	51.6 ± 0.2	51.5 ± 0.2	51.7 ± 0.1	51.5 ± 0.2	51.5 ± 0.2	50.9 ± 0.2
Mean cell hemoglobin (pg)						
Day 4	20.1 ± 0.1	20.1 ± 0.1	20.1 ± 0.1	20.0 ± 0.1	19.7 ± 0.2	19.8 ± 0.1*
Day 21	20.1 ± 0.1	20.1 ± 0.2	20.4 ± 0.1	20.3 ± 0.1	19.7 ± 0.1*	19.6 ± 0.1**
Week 14	17.0 ± 0.1	17.0 ± 0.1	17.1 ± 0.1	17.2 ± 0.1	17.0 ± 0.1	16.9 ± 0.1
Platelets (10^3/μL)						
Day 4	875.8 ± 15.7	920.8 ± 25.7	909.1 ± 13.9	939.0 ± 26.3	868.7 ± 18.5	828.5 ± 24.5
Day 21	869.2 ± 18.6	883.7 ± 13.5	859.6 ± 17.0	894.3 ± 19.7	836.8 ± 9.9	742.2 ± 14.8**
Week 14	636.1 ± 9.9	629.0 ± 14.2	634.7 ± 12.6	646.5 ± 8.9	610.8 ± 8.5	572.2 ± 12.3**
Clinical Chemistry						
n	10	10	10	10	10	10
Total protein (g/dL)						
Day 4	5.5 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.4 ± 0.1	5.2 ± 0.0*	4.9 ± 0.1**
Day 21	6.3 ± 0.1	6.5 ± 0.1	6.6 ± 0.1*	6.5 ± 0.1	6.5 ± 0.1	6.0 ± 0.1
Week 14	6.7 ± 0.0	6.8 ± 0.1	6.9 ± 0.1*	6.9 ± 0.1*	7.0 ± 0.1**	6.9 ± 0.1**
Albumin (g/dL)						
Day 4	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	3.9 ± 0.0	3.8 ± 0.1*
Day 21	4.5 ± 0.0	4.7 ± 0.1	4.7 ± 0.1*	4.7 ± 0.1	4.7 ± 0.1*	4.5 ± 0.1
Week 14	4.8 ± 0.0	4.9 ± 0.1*	5.1 ± 0.1**	5.0 ± 0.1**	5.1 ± 0.0**	5.2 ± 0.1**
Alkaline phosphatase (IU/L)						
Day 4	745 ± 17	754 ± 14	769 ± 25	805 ± 22*	818 ± 17*	788 ± 17*
Day 21	556 ± 8	509 ± 11**	515 ± 16*	516 ± 11*	504 ± 19**	479 ± 7**
Week 14	200 ± 10	182 ± 4	201 ± 10	174 ± 9	186 ± 6	192 ± 6
Bile acids (μmol/L)						
Day 4	34.9 ± 3.1	33.9 ± 2.2	35.9 ± 2.2	38.0 ± 2.7	52.8 ± 3.3**	53.2 ± 2.9**
Day 21	24.9 ± 1.5	26.2 ± 1.2	31.7 ± 1.4**	26.0 ± 0.9	29.0 ± 1.7	24.2 ± 1.1
Week 14	20.4 ± 2.1	16.6 ± 1.7	13.6 ± 0.7*	18.5 ± 1.7	17.8 ± 1.9	16.9 ± 1.5

TABLE 4
Selected Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Female						
Hematology						
n						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	9	9	10
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 4	43.5 ± 0.6	44.5 ± 0.5	45.1 ± 0.7	45.8 ± 1.2	45.5 ± 0.7	46.6 ± 1.0
Day 21	46.2 ± 0.3	45.4 ± 0.4	44.9 ± 0.5	46.8 ± 0.7	44.2 ± 0.4**	43.4 ± 0.8**
Week 14	42.4 ± 0.3	42.9 ± 0.4	42.7 ± 0.3	42.4 ± 0.5	41.5 ± 0.5	40.9 ± 0.5
Hemoglobin (g/dL)						
Day 4	14.3 ± 0.2	14.6 ± 0.2	14.8 ± 0.3	15.2 ± 0.4	15.1 ± 0.3	15.4 ± 0.3
Day 21	15.6 ± 0.1	15.3 ± 0.2	15.3 ± 0.2	15.7 ± 0.2	15.0 ± 0.2*	14.7 ± 0.2**
Week 14	13.7 ± 0.1	13.9 ± 0.1	13.9 ± 0.1	13.8 ± 0.1	13.5 ± 0.2	13.2 ± 0.1*
Erythrocytes (10^6/µL)						
Day 4	7.53 ± 0.11	7.71 ± 0.12	7.76 ± 0.15	7.96 ± 0.19	7.90 ± 0.14	8.23 ± 0.16**
Day 21	7.98 ± 0.07	7.77 ± 0.06	7.70 ± 0.10	8.08 ± 0.13	7.73 ± 0.13	7.79 ± 0.15
Week 14	8.07 ± 0.05	8.11 ± 0.05	8.13 ± 0.05	8.13 ± 0.10	8.06 ± 0.09	7.97 ± 0.08
Mean cell volume (fL)						
Day 4	57.8 ± 0.3	57.8 ± 0.4	58.2 ± 0.3	57.5 ± 0.2	57.7 ± 0.3	56.7 ± 0.5
Day 21	57.9 ± 0.3	58.4 ± 0.5	58.4 ± 0.2	58.0 ± 0.5	57.2 ± 0.6	55.7 ± 0.3**
Week 14	52.5 ± 0.2	53.0 ± 0.2	52.6 ± 0.2	52.1 ± 0.2	51.5 ± 0.2*	51.3 ± 0.2**
Mean cell hemoglobin (pg)						
Day 4	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	18.7 ± 0.1
Day 21	19.6 ± 0.1	19.7 ± 0.1	19.9 ± 0.1	19.5 ± 0.1	19.4 ± 0.1	18.9 ± 0.1**
Week 14	17.0 ± 0.1	17.1 ± 0.1	17.2 ± 0.1	17.0 ± 0.1	16.7 ± 0.1*	16.6 ± 0.1*
Platelets (10^3/µL)						
Day 4	766.0 ± 19.4	802.3 ± 23.6	800.1 ± 24.8	794.9 ± 25.8	820.2 ± 21.1	744.6 ± 12.5
Day 21	722.9 ± 19.2	815.3 ± 24.9	803.8 ± 14.8	806.1 ± 25.1	754.4 ± 22.4	705.3 ± 19.8
Week 14	690.2 ± 15.6	661.5 ± 10.5	689.0 ± 15.4	674.7 ± 10.7	660.1 ± 13.9	608.2 ± 10.9**
Clinical Chemistry						
n						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	8	9	10
Week 14	10	10	10	10	10	10
Total protein (g/dL)						
Day 4	5.6 ± 0.1	5.6 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.3 ± 0.1	5.2 ± 0.1*
Day 21	6.2 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.6 ± 0.1*	6.7 ± 0.1**	6.4 ± 0.1*
Week 14	6.7 ± 0.1	7.1 ± 0.1*	7.4 ± 0.1**	7.3 ± 0.1**	7.5 ± 0.1**	7.4 ± 0.1**
Albumin (g/dL)						
Day 4	4.1 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Day 21	4.6 ± 0.1	4.8 ± 0.1*	4.8 ± 0.1*	4.9 ± 0.1**	5.1 ± 0.1**	5.0 ± 0.1**
Week 14	5.2 ± 0.2	5.6 ± 0.1*	5.9 ± 0.1**	5.8 ± 0.1**	6.0 ± 0.1**	5.9 ± 0.1**
Alkaline phosphatase (IU/L)						
Day 4	550 ± 13	596 ± 24	582 ± 15	642 ± 25**	674 ± 31**	613 ± 26**
Day 21	374 ± 10	355 ± 8	341 ± 12*	356 ± 10	317 ± 9**	302 ± 10**
Week 14	165 ± 8	162 ± 7	162 ± 6	152 ± 5	149 ± 5	142 ± 6*
Bile acids (µmol/L)						
Day 4	21.5 ± 2.0	22.9 ± 2.2	25.1 ± 2.1	25.9 ± 1.9	32.9 ± 3.3**	44.8 ± 4.8**
Day 21	24.0 ± 2.4	17.5 ± 0.9*	20.3 ± 1.2	20.4 ± 1.6	18.2 ± 0.9	18.1 ± 0.7
Week 14	22.9 ± 2.1	25.6 ± 2.9	20.7 ± 2.7	22.5 ± 2.8	23.0 ± 3.1	24.9 ± 2.8

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

Cell proliferation in the liver of 1,000 and 2,000 mg/L male rats, but not in female rats, was significantly greater than in the controls (Table 5). Eight of 10 males in the 1,000 mg/L group had labeling indices greater than the highest individual control value (data not shown). The biological significance of this difference is not clear since the increases were not dose-related and increases in liver weights were the same for male and female rats.

Treatment-related histopathological changes were noted in the liver, pituitary gland, epididymis, testes, and spleen. Although treatment-related organ weight changes were noted in the kidney, heart, lung, and thymus, no corresponding microscopic changes were noted.

Testicular atrophy was noted in the 2,000 mg/L group, and retained spermatids were observed in the 500 and 1,000 mg/L groups; 250 mg/L was the no-observed-effect level (NOEL) for testicular lesions (Table 6; Plates 1 and 2). Testicular atrophy was characterized by marked degeneration/loss of germinal epithelium, giant/syncytial cell formation, vacuolation of Sertoli cells, mild nonsuppurative inflammation around some venules, and more prominent interstitial cells. The testicular atrophy correlated with the decreased right testis weight noted in this group. Gradation of the testicular lesions was as follows: minimal (grade 1), depletion of approximately 5% or less of germinal epithelium; mild (grade 2), depletion of approximately 6% to 20% of germinal epithelium; moderate (grade 3), depletion of approximately 21% to 50% of germinal epithelium; marked (grade 4), depletion of approximately 51% or greater of germinal epithelium. Hypospermia was significantly increased in the epididymis, and sperm motility and spermatid heads were significantly reduced in 2,000 mg/L males (Tables 6 and H1).

Testicular changes seen in groups treated with 500 and 1,000 mg/L were similar to those seen in the 14-day study. The lesions were characterized by delays in spermiation. Step 19 spermatids were retained and found in the outermost part of the seminiferous epithelium adjacent to the lumen in stages IX and X of the spermatogenic cycle. These changes were occasionally accompanied by large residual bodies. The overall severity of the lesions was mild.

In the pituitary gland of male rats exposed to 2,000 mg/L, cellular hypertrophy was noted (Table 6). This alteration was characterized by increased cytoplasmic pallor, enlargement, and vacuolation of the cells of the pituitary gland pars distalis. This change is considered to be secondary to the testicular atrophy. The hypertrophic cells are commonly called "castration cells" and were seen following orchiectomy, considered to be due to hypertrophy of the FSH LH secreting cells (MacKenzie and Boorman, 1990).

TABLE 5
BrdU Labeling Index in the Liver of Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male				
Labeling Index (%)	0.20 ± 0.10	1.07 ± 1.29	0.48 ± 0.26**	0.77 ± 0.48*
Female				
Labeling Index (%)	0.93 ± 0.37	0.83 ± 0.40[b]	1.16 ± 0.71[b]	0.88 ± 0.66

* Significantly different ($P \leq 0.05$) from the control group by Student's *t*-test
** $P \leq 0.01$
[a] Data are presented as mean ± standard deviation (n=10).
[b] n=9

TABLE 6
Incidences of Selected Nonneoplastic Lesions in Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L		125 mg/L		250 mg/L		500 mg/L		1,000 mg/L		2,000 mg/L	
Male												
Testes[a]	10		10		10		10		10		10	
Delayed Spermiation, Retained Spermatids[b]	0		0		0		8**	(1.6)[c]	8**	(2.0)	0	
Germinal Epithelium, Atrophy	0		0		0		0		0		10**	(3.4)
Epididymis	10		10		10		10		10		9	
Hypospermia	0		0		0		0		0		9**	(3.1)
Pituitary Gland	10		10		10		10		10		10	
Pars Distalis, Hypertrophy	1	(1.0)	0		0		0		0		6*	(1.3)
Liver	10		10		10		10		10		10	
Hepatocyte, Vacuolization, Cytoplasmic	3	(1.0)	5	(1.0)	7	(1.0)	9*	(1.3)	9*	(1.3)	10**	(2.0)
Female												
Liver	10		10		10		10		10		10	
Hepatocyte, Vacuolization, Cytoplasmic	0		0		1	(1.0)	0		3	(1.0)	10**	(1.5)
Spleen	10		10		10		10		10		10	
Hematopoietic Cell Proliferation	0		0		0		0		0		4*	(1.3)

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

In the liver, an exposure concentration-related increase in the centrilobular to midzonal glycogen-like hepatocellular vacuolization was noted in males in all exposed groups and in females in the 1,000 and 2,000 mg/L groups (Table 6). Involvement was characterized as minimal to mild.

In the spleen, minimal to mild hematopoietic cell proliferation was noted in females in the 2,000 mg/L group (Table 6). This change was characterized by minimal increases in the myeloid and erythroid precursors in the red pulp.

Exposure Concentration Selection Rationale: Based on decreased body weight gain, organ weight effects, and severity of testicular lesions observed at 2,000 mg/L, dibromoacetic acid exposure concentrations selected for the 2-year drinking water study in rats were 50, 500, and 1,000 mg/L.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 2). Treatment with dibromoacetic acid had no effect on survival of male or female rats.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of 1,000 mg/L males and females were less than those of the controls after week 29 and week 49, respectively, and those of 500 mg/L males were less after week 57 (Figure 3; Tables 8 and 9). Water consumption by males and females exposed to 1,000 mg/L was less than that by controls during year 2 of the study (Tables J1 and J2). Drinking water concentrations of 50, 500, and 1,000 mg/L resulted in average daily doses of approximately 2, 20, and 40 mg/kg to males and 2, 25, and 45 mg/kg to females.

TABLE 7
Survival of Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	4	15	12	12
Natural deaths	12	11	8	9
Animals surviving to study termination	34	24	30[e]	28
Percent probability of survival at end of study[b]	68	48	60	57
Mean survival (days)[c]	683	676	652	666
Survival analysis[d]	P=0.784	P=0.092	P=0.406	P=0.332
Female				
Animals initially in study	50	50	50	50
Moribund	4	5	9	14
Natural deaths	11	6	6[f]	4
Animals surviving to study termination	35	39[f]	35	32
Percent probability of survival at end of study	70	78	70	64
Mean survival (days)	690	705	693	683
Survival analysis	P=0.232	P=0.427N	P=1.000N	P=0.674

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A lower mortality in an exposed group is indicated by **N**.
[e] Includes three animals that died during the last week of the study
[f] Includes one animal that died during the last week of the study

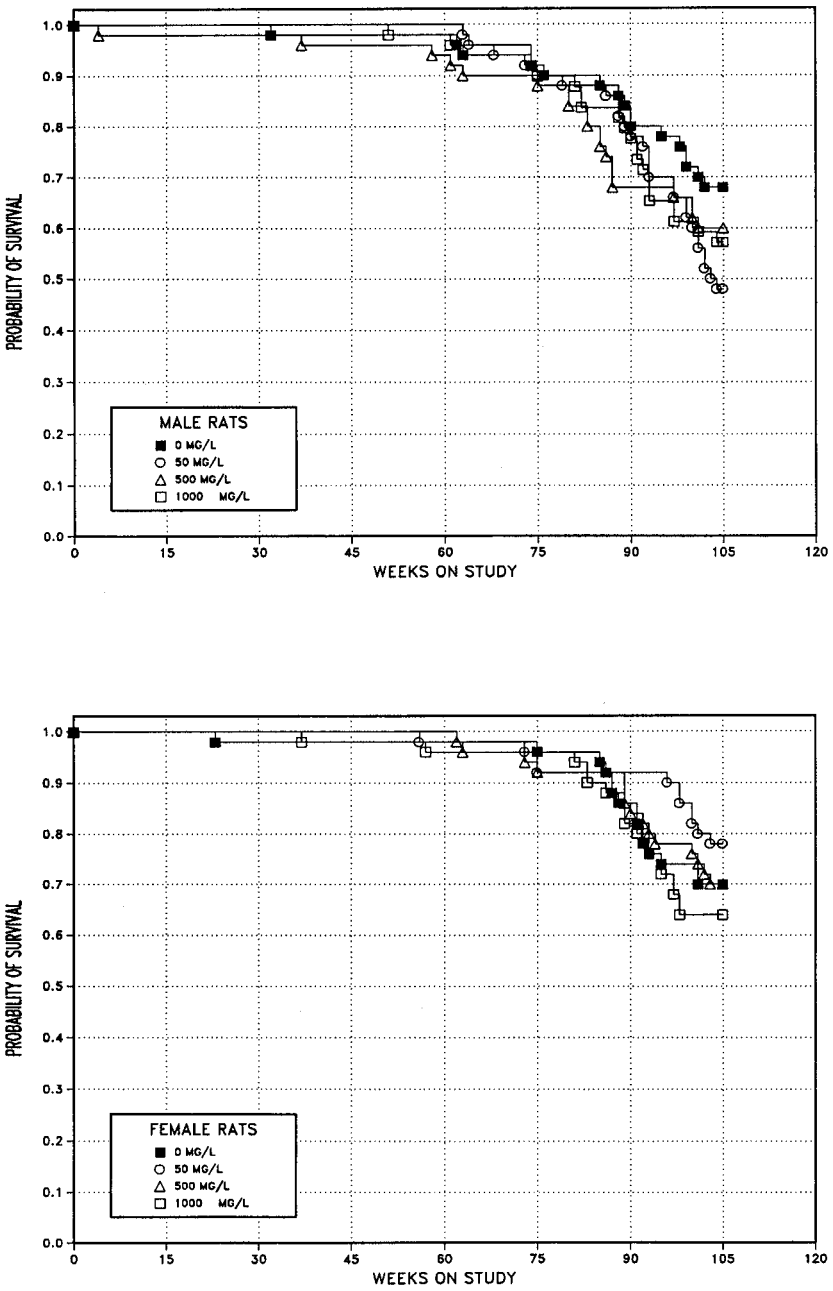


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Dibromoacetic Acid in Drinking Water for 2 Years

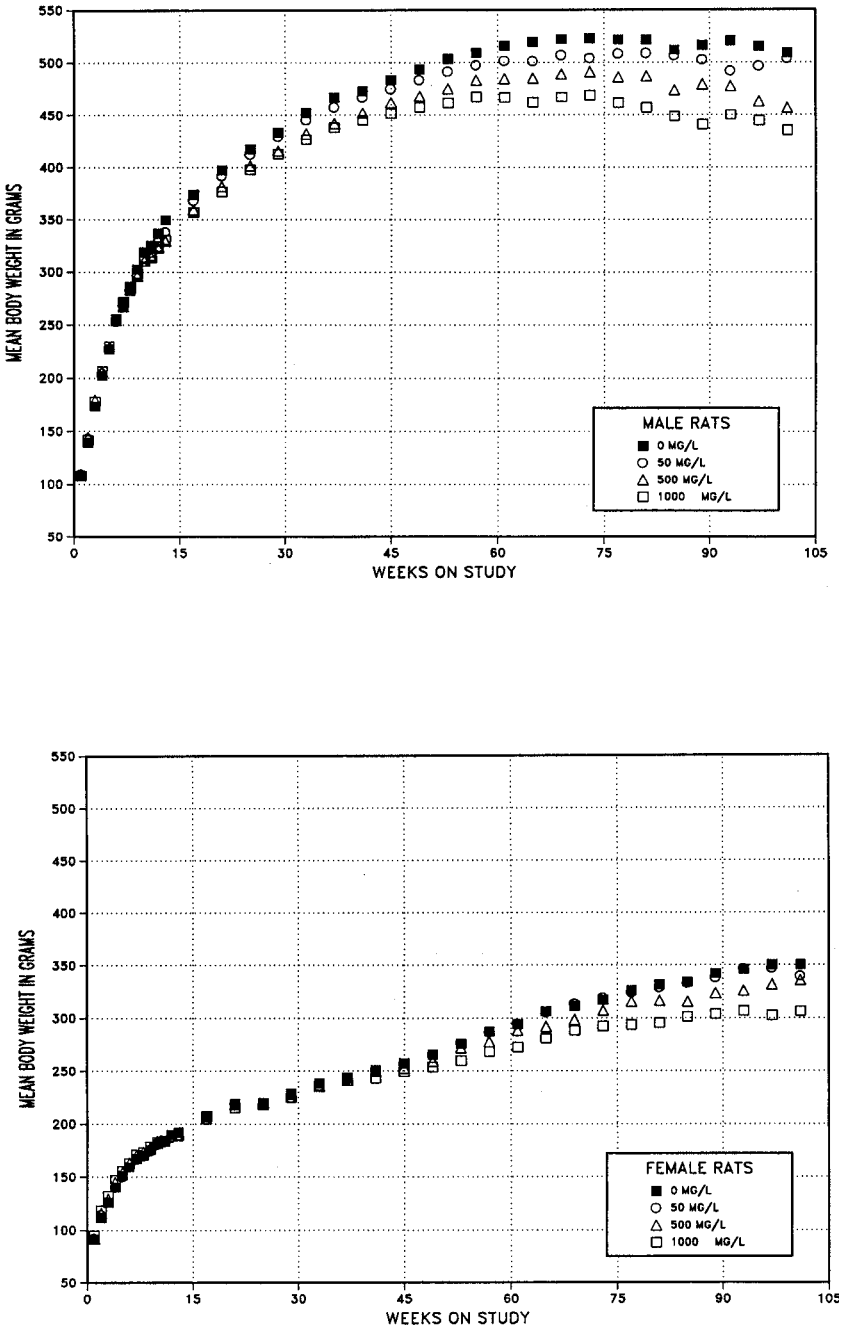


FIGURE 3
Growth Curves for Male and Female Rats Exposed to Dibromoacetic Acid in Drinking Water for 2 Years

TABLE 8
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

Weeks on Study	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	108	50	110	102	50	110	102	50	108	101	50
2	140	50	143	103	50	145	104	50	142	102	50
3	174	50	173	100	50	179	103	50	178	102	50
4	203	50	205	101	50	206	102	49	206	102	50
5	227	50	227	100	50	229	101	49	230	101	50
6	254	50	253	99	50	255	100	49	255	100	50
7	271	50	268	99	50	268	99	49	272	100	50
8	286	50	283	99	50	283	99	49	285	100	50
9	303	50	296	98	50	296	98	49	299	99	50
10	319	50	314	98	50	311	97	49	313	98	50
11	325	50	319	98	50	314	97	49	316	97	50
12	337	50	329	98	50	323	96	49	325	96	50
13	350	50	338	97	50	330	94	49	331	95	50
17	374	50	368	99	50	360	96	49	357	96	50
21	398	50	392	99	50	382	96	49	377	95	50
25	418	50	413	99	50	401	96	49	398	95	50
29	434	50	430	99	50	416	96	49	413	95	50
33	452	49	445	99	50	432	96	49	427	94	50
37	467	49	458	98	50	442	95	49	438	94	50
41	473	49	467	99	50	452	96	48	445	94	50
45	484	49	475	98	50	462	96	48	452	94	50
49	494	49	484	98	50	468	95	48	457	93	50
53	503	49	491	98	50	475	94	48	462	92	49
57	509	49	498	98	50	483	95	48	467	92	48
61	516	49	501	97	50	485	94	47	467	91	48
65	519	47	501	97	48	485	93	45	462	89	47
69	522	47	507	97	47	489	94	45	467	90	47
73	523	47	504	96	47	491	94	45	469	90	47
77	522	45	508	98	45	486	93	44	462	89	44
81	522	45	509	98	44	487	93	42	457	88	43
85	512	45	506	99	44	474	93	40	449	88	41
89	516	43	503	97	41	479	93	34	441	85	40
93	521	40	492	95	38	477	92	34	450	87	35
97	515	39	496	96	35	463	90	34	445	86	32
101	509	36	504	99	30	457	90	31	435	86	30
Mean for weeks											
1-13	254		251	99		250	99		251	99	
14-52	444		437	99		424	96		418	94	
53-101	516		502	97		479	93		456	89	

TABLE 9
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

Weeks on Study	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	92	50	92	101	50	92	101	50	95	104	50
2	112	50	114	102	50	116	104	50	119	106	50
3	126	50	126	100	50	130	103	50	132	105	50
4	140	50	140	100	50	145	103	50	147	105	50
5	152	50	150	99	50	154	102	50	156	103	50
6	160	50	159	100	50	163	102	50	163	102	50
7	167	50	166	99	50	170	102	50	171	102	50
8	171	50	170	99	50	174	102	50	173	102	50
9	176	50	174	99	50	178	101	50	179	102	50
10	181	50	181	100	50	184	102	50	183	101	50
11	185	50	183	99	50	184	100	50	184	100	50
12	190	50	187	98	50	189	99	50	189	99	50
13	192	50	189	98	50	190	99	50	189	98	50
17	207	50	204	99	50	205	99	50	207	100	50
21	219	50	219	100	50	219	100	50	215	98	50
25	220	49	218	99	50	220	100	50	218	99	50
29	229	49	225	98	50	228	100	50	225	98	50
33	239	49	235	99	50	236	99	50	236	99	50
37	244	49	242	99	50	242	99	50	241	99	49
41	251	49	251	100	50	250	100	50	243	97	49
45	258	49	257	100	50	252	98	50	249	97	49
49	265	49	265	100	50	259	98	50	254	96	49
53	276	49	276	100	50	272	99	50	260	94	49
57	287	49	286	100	49	278	97	50	268	93	49
61	294	49	295	100	49	288	98	50	272	93	48
65	306	49	305	100	49	292	95	48	281	92	48
69	312	49	313	101	49	298	96	48	288	93	48
73	317	49	319	101	49	307	97	47	292	92	48
77	326	48	324	99	46	316	97	46	294	90	48
81	332	48	329	99	46	317	95	46	296	89	48
85	334	48	333	100	46	316	95	46	301	90	45
89	342	43	338	99	46	324	95	45	304	89	44
93	346	39	347	100	46	326	94	41	307	89	40
97	350	37	347	99	45	332	95	39	303	86	36
101	351	35	340	97	40	336	96	37	306	87	32
Mean for weeks											
1-13	157		156	100		159	102		160	102	
14-52	237		235	99		235	99		232	98	
53-101	321		319	100		308	96		290	91	

Toxicokinetics

After a single gavage dose of dibromoacetic acid (25, 50, or 125 mg/kg) to male and female F344/N rats, the plasma concentration versus time data can be described by a one-compartment model with no lag phase and first-order absorption and elimination for both males and females (Appendix N). A comparison of the absorption and elimination rate constants for all three gavage dose groups to the elimination rate constant following a single intravenous administration of 25 mg/kg indicated that the gavage profiles were characteristic of a flip-flop model, where the initial upward phase of the profile is a measure of elimination and the terminal linear phase actually reflects absorption. The elimination half-life was approximately 6 to 12 minutes. Calculated values for clearance, volume of distribution, and area under the plasma concentration versus time curves (AUC) extrapolated to infinity were not accurate due to the flip-flop kinetics; however, the $AUC_{0\text{-}1\ hour}$ values were not affected by extrapolation in the terminal linear phase. This parameter increased with increasing dose, and the increase was approximately dose-proportional. Bioavailability increased with dose and ranged from approximately 43% to 61% for males and 64% to 91% for females.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant mesothelioma and mononuclear cell leukemia and neoplasms or nonneoplastic lesions of the liver, lung, kidney, and pituitary gland. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Malignant Mesothelioma: The incidence of malignant mesothelioma in male rats was significantly increased in the 1,000 mg/L group (Tables 10 and A3). The incidence in the 1,000 mg/L group exceeded the historical range in controls from drinking water studies (Tables 10 and A4a). Mesothelioma was seen on the abdominal wall and serosal surface of several abdominal organs (e.g., mesentery, peritoneum, testes, epididymis, prostate and seminal vesicles, pancreas, adrenal gland, spleen, mesenteric lymph nodes, kidney, urinary bladder, stomach, and skeletal muscle). The distinction between

TABLE 10
Incidences of Malignant Mesothelioma in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Malignant Mesothelioma[a]				
Overall rate[b]	3/50 (6%)	1/50 (2%)	0/50 (0%)	10/50 (20%)
Adjusted rate[c]	6.9%	2.4%	0.0%	22.6%
Terminal rate[d]	2/34 (6%)	1/24 (4%)	0/30 (0%)	2/28 (7%)
First incidence (days)	591	729 (T)	—[f]	512
Poly-3 test[e]	P<0.001	P=0.325N	P=0.137N	P=0.035

(T) Terminal sacrifice
[a] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 15/250 (6.0% ± 4.2%), range 0%-12%
[b] Number of neoplasm-bearing animals/number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group

benign and malignant mesothelioma is not clear (Hall, 1990). Because neoplastic cells were found throughout the peritoneum, all mesotheliomas were classified as malignant.

Microscopically, mesothelioma consisted of exophytic, papillary projections of one or more layers of plump, cuboidal mesothelial cells with prominent, basophilic, round nuclei and abundant eosinophilic to amphophilic cytoplasm, on a supporting pedunculated, fibrovascular stromal stalk (Plates 3 and 4). The amount of the stromal component varied considerably, and at times the pleomorphic mesothelial cells took on a tubular appearance or occurred in packets that were densely packed. In NTP studies, chemically induced mesotheliomas have been seen almost exclusively in male rats.

Mononuclear Cell Leukemia: A positive trend in the incidence of mononuclear cell leukemia occurred in female rats (Tables 11 and B3), and the incidence in 1,000 mg/L females was significantly increased. A significant increase in mononuclear cell leukemia also occurred in 50 mg/L males (Tables 11 and A3). The incidences of mononuclear cell leukemia in 50 and 500 mg/L males and in 500 and 1,000 mg/L females exceeded the historical control ranges from drinking water studies (Tables 11, A4b, and B4). Mononuclear cell leukemia is one of the most common spontaneously occurring hematopoietic system neoplasms seen in F344/N rats. Mononuclear cell leukemia is a rapidly progressive, lethal neoplastic disease that first develops in the spleen, with infiltrates of neoplastic cells also occurring in the liver, lung, lymph nodes, bone marrow, and most other organs (Elwell *et al.*, 1996). There was no evidence of splenic toxicity in males; hence, the decrease in mononuclear cell leukemia incidence in the 1,000 mg/L group compared to that in the 50 mg/L group was not due to toxicity in the spleen at the higher exposure concentration.

TABLE 11
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Mononuclear Cell Leukemia[a]				
Overall rate[b]	17/50 (34%)	31/50 (62%)	24/50 (48%)	13/50 (26%)
Adjusted rate[c]	37.0%	66.2%	56.2%	30.2%
Terminal rate[d]	11/34 (32%)	15/24 (63%)	16/30 (53%)	5/28 (18%)
First incidence (days)	437	446	423	386
Poly-3 test[e]	P=0.026N	P=0.003	P=0.051	P=0.325N
Female				
Mononuclear Cell Leukemia[f]				
Overall rate	11/50 (22%)	13/50 (26%)	16/50 (32%)	22/50 (44%)
Adjusted rate	24.3%	27.1%	34.7%	47.4%
Terminal rate	8/35 (23%)	8/39 (21%)	11/35 (31%)	12/32 (38%)
First incidence (days)	605	509	519	395
Poly-3 test	P=0.006	P=0.474	P=0.195	P=0.016

[a] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 79/250 (31.6% ± 3.3%), range 26%-34%
[b] Number of neoplasm-bearing animals/number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[f] Historical incidence: 47/200 (23.5% ± 4.4%), range 20%-30%

Liver: The incidences of cystic degeneration in male rats were significantly increased in all exposed groups (Tables 12 and A5). However, the overall change was minimal to mild. Microscopically, this change consisted of focal areas of severe hepatocytic vacuolization in which a number of adjacent hepatocytes had ruptured and coalesced, forming large cystic spaces containing a faintly eosinophilic, flocculent material.

Lung: The incidences of alveolar epithelial hyperplasia were significantly increased in 500 and 1,000 mg/L females (Tables 12 and B4). Microscopically, hyperplasia of alveolar epithelium consisted of focal thickening of the alveolar septa caused by increased numbers of prominent, cuboidal type II pneumocytes, with maintenance of normal alveolar septal architecture. There was a marginal increase in the incidence of alveolar/bronchiolar adenoma or carcinoma in 1,000 mg/L females (2/50, 3/50, 2/50, 5/50; Table B3), and the incidence exceeded the historical control range for 2-year drinking water studies [8/200 (4.0% ± 1.6%), range 2%-6%].

Kidney: The incidences of nephropathy were significantly increased in all exposed groups of females (Tables 12 and B4). Nephropathy consisted of focal to multifocal regenerative renal tubules surrounded by a thickened basement membrane, glomerular thickening, tubular protein casts, and chronic inflammatory infiltrates with fibrosis. In a number of cases graded minimal, the lesions consisted almost exclusively of a few tubular protein casts.

Pituitary Gland: The incidence of pars distalis adenoma was significantly decreased in 1,000 mg/L males (23/50, 21/49, 17/49, 8/50; Table A3). The incidence of adenoma in 1,000 mg/L males was less than the range in historical controls [89/244 (36.4% ± 8.7%), range 26%-46%] while that in the control group was at the upper end of the historical control range.

TABLE 12
Incidences of Selected Nonneoplastic Lesions in Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Liver[a]	50	50	50	50
Degeneration, Cystic[b]	3 (1.0)[c]	9* (1.4)	11* (1.5)	15** (1.3)
Female				
Lung	50	50	50	50
Alveolar Epithelium, Hyperplasia	3 (1.3)	7 (1.9)	13** (1.7)	14** (1.9)
Kidney	50	50	50	50
Nephropathy	18 (1.1)	32** (1.3)	37** (1.4)	40** (1.3)

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

MICE

2-WEEK STUDY

All mice survived to the end of the study (Table 13). Final mean body weights of male and female mice were similar to those of the controls; mean body weight gains of 250 and 500 mg/L males were significantly greater than that of the controls. Water consumption by exposed and control groups was similar. Drinking water concentrations of 0, 125, 250, 500, 1,000, and 2,000 mg/L resulted in average daily doses of approximately 0, 24, 47, 95, 178, and 370 mg dibromoacetic acid/kg body weight to males and 0, 22, 53, 88, 166, and 309 mg/kg to females. There were no clinical findings related to dibromoacetic acid exposure.

Liver weights of males in the 1,000 and 2,000 mg/L groups and females in the 500, 1,000, and 2,000 mg/L groups were significantly increased (Table G3). Thymus weights of males and females in the 1,000 and 2,000 mg/L groups were significantly decreased compared to controls. Gross lesions observed in the thymus and liver of male and female mice were considered to be related to exposure to dibromoacetic acid.

The incidences of thymus atrophy were increased in males exposed to 1,000 or 2,000 mg/L and in 2,000 mg/L females (males: 0 mg/L, 0/5; 125 mg/L, 0/5; 250 mg/L, 0/5; 500 mg/L, 0/5; 1,000 mg/L, 4/5; 2,000 mg/L, 5/5; females: 0/5, 0/5, 0/5, 0/5, 0/5, 5/5). This lesion consisted of a minimal to mild decrease in the thickness of the thymic cortex.

The incidences of morphological changes to the germinal epithelium in the testis were significantly increased in males exposed to 1,000 or 2,000 mg/L (0/5, 0/5, 0/5, 1/5, 5/5, 5/5). This change was characterized by the presence of large (15 to 35 microns) round to oval

TABLE 13
Survival, Body Weights, and Water Consumption of Mice in the 2-Week Drinking Water Study of Dibromoacetic Acid

Concentration (mg/L)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	22.4 ± 0.4	25.2 ± 0.4	2.8 ± 0.3		4.3	4.6
125	5/5	22.0 ± 0.5	24.4 ± 0.6	2.5 ± 0.3	97	4.2	4.4
250	5/5	21.6 ± 0.4	25.5 ± 0.4	3.8 ± 0.2*	101	4.4	4.2
500	5/5	22.6 ± 0.4	26.4 ± 0.4	3.8 ± 0.2*	105	4.4	4.6
1,000	5/5	22.5 ± 0.3	25.7 ± 0.3	3.2 ± 0.2	102	4.2	4.1
2,000	5/5	21.5 ± 0.4	24.5 ± 0.4	3.0 ± 0.2	97	4.1	4.1
Female							
0	5/5	18.7 ± 0.2	20.5 ± 0.4	1.9 ± 0.4		3.2	3.5
125	5/5	18.5 ± 0.5	20.5 ± 0.3	1.9 ± 0.4	100	3.4	3.1
250	5/5	18.6 ± 0.3	20.6 ± 0.3	1.9 ± 0.2	100	3.5	4.7
500	5/5	18.7 ± 0.4	21.0 ± 0.4	2.3 ± 0.4	102	3.1	3.7
1,000	5/5	18.7 ± 0.3	21.4 ± 0.3	2.7 ± 0.3	104	3.0	3.4
2,000	5/5	18.5 ± 0.3	20.9 ± 0.4	2.4 ± 0.2	102	2.8	3.1

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Water consumption is expressed as grams per animal per day.

amphophilic to eosinophilic bodies (interpreted as atypical residual bodies) in seminiferous tubules, and occasional spermatid retention. The atypical residual bodies were present free in the lumen and also near the basement membrane of the seminiferous tubules.

Exposure Concentration Selection Rationale: Based on lack of lethality, clinical signs of toxicity, and body weight changes, dibromoacetic acid exposure concentrations selected for the 3-month drinking water study in mice were 125, 250, 500, 1,000, and 2,000 mg/L.

3-Month Study

All mice survived to the end of the study (Table 14). Final mean body weights of 2,000 mg/L females and body weight gains of 2,000 mg/L males and females were significantly less than those of the controls. Water consumption by males in the 2,000 mg/L group was decreased at weeks 1 and 13 relative to control mice. Drinking water concentrations of 125, 250, 500, 1,000, and 2,000 mg/L resulted in average daily doses of approximately 16, 30, 56, 115, and 230 mg dibromoacetic acid/kg body weight to males and 17, 34, 67, 132, and 260 mg/kg to females. There were no clinical findings related to dibromoacetic acid exposure.

The hematology data for mice in the 3-month toxicity study of dibromoacetic acid are listed in Table F2. In general, mice were affected much less than rats when administered the same exposure concentrations of dibromoacetic acid. Of the erythron effects observed in the rats, only the mean cell hemoglobin values demonstrated a similar decrease. This change was small (~3%) and only occurred in the 2,000 mg/L male mice. Small decreases in platelet counts (~16%) and white blood cell counts (~23%) in the 2,000 mg/L male mice were also observed in rats. Other changes in the hematological variables in male mice were not considered toxicologically relevant; no changes occurred in female mice.

Table 14
Survival, Body Weights, and Water Consumption of Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid

Concentration (mg/L)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	23.0 ± 0.3	38.2 ± 1.1	15.2 ± 0.9		4.4	3.7
125	10/10	22.9 ± 0.2	39.1 ± 0.6	16.3 ± 0.6	102	4.0	3.5
250	10/10	23.6 ± 0.2	40.1 ± 0.4	16.5 ± 0.4	105	4.2	3.6
500	10/10	22.7 ± 0.5	39.6 ± 1.0	17.0 ± 0.9	104	4.0	3.1
1,000	10/10	23.1 ± 0.2	37.6 ± 0.9	14.4 ± 1.0	98	4.1	3.1
2,000	10/10	23.1 ± 0.2	35.1 ± 1.1	12.0 ± 1.1*	92	3.8	2.9
Female							
0	10/10	18.4 ± 0.2	30.0 ± 1.2	11.6 ± 1.0		3.2	3.0
125	10/10	18.4 ± 0.3	30.4 ± 1.0	12.0 ± 0.9	101	3.0	3.0
250	10/10	18.6 ± 0.2	30.5 ± 0.8	11.9 ± 0.8	102	3.0	3.1
500	10/10	18.7 ± 0.2	29.7 ± 0.8	10.9 ± 0.9	99	3.0	2.9
1,000	10/10	18.2 ± 0.4	29.5 ± 0.6	11.3 ± 0.7	98	3.1	3.1
2,000	10/10	18.7 ± 0.3	26.5 ± 0.6**	7.8 ± 0.6**	88	2.6	3.0

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Water consumption is expressed as grams per animal per day.

Lung weights were increased in 1,000 and 2,000 mg/L females. Liver weights of males and females exposed to 500 mg/L or greater were significantly increased (Table G4).

There were no significant increases between exposed and control mice in BrdU labeling index in the liver (Table 15); the decrease in 2,000 mg/L males was not considered biologically significant.

Hepatocellular cytoplasmic vacuolization was present in most mice, and the severity was increased in 1,000 and 2,000 mg/L males and females [males: 0 mg/L, 10/10 (1.6); 125 mg/L, 9/10 (1.6); 250 mg/L, 10/10 (1.5); 500 mg/L, 10/10 (1.5); 1,000 mg/L, 10/10 (2.1); 2,000 mg/L, 10/10 (2.9); females: 10/10 (1.5), 10/10 (1.5), 8/8 (1.5), 10/10 (1.7), 10/10 (2.3), 10/10 (2.7)]. The increased severity of vacuolization correlated in general with the increased liver weight. No corresponding liver morphological change to explain the statistically significant increased organ weight was noted in the 500 mg/L group. The cytoplasmic vacuoles were more accentuated in the periportal regions and had morphological characteristics suggestive of glycogen, such as ragged outline and no displacement of the nuclei.

The incidences of abnormal testicular morphology were significantly increased in 1,000 and 2,000 mg/L males [0/10, 0/10, 0/10, 0/10, 9/10 (1.0), 10/10 (2.0)]. This change was characterized by the presence of large (15 to 35 micron) round to oval amphophilic to eosinophilic bodies (interpreted as atypical residual bodies) in seminiferous tubules, occasional spermatid retention, and rare vacuolization of Sertoli cells (Plates 5 and 6). The atypical residual bodies were present free in the lumen and also near the basement membrane of the seminiferous tubules. They were also observed in the head and tail of the epididymis. The severity grades for this change were based upon the extent of atypical residual bodies within seminiferous tubules, with minimal severity representing only a few atypical residual bodies within scattered tubules and marked severity representing many atypical residual bodies within a majority of tubules. The change in the epididymis is considered to represent downstream collection of cells from the testes. There was no effect on epididymal sperm concentration, sperm motility, or spermatid heads (Table H3).

Exposure Concentration Selection Rationale: Based on decreased body weight gain and the severity of microscopic lesions at 2,000 mg/L, dibromoacetic acid exposure concentrations selected for the 2-year drinking water study in mice were 50, 500, and 1,000 mg/L.

TABLE 15
BrdU Labeling Index in the Liver of Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male				
Labeling Index (%)	0.71 ± 0.24	0.40 ± 0.20	0.53 ± 0.33	0.28 ± 0.15*
Female				
Labeling Index (%)	2.58 ± 1.09	2.12 ± 1.41	1.96 ± 0.70	1.82 ± 1.96

* Significantly different ($P \leq 0.05$) from the control group by Student's *t*-test
[a] Data are presented as mean ± standard deviation (n=10).

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 16 and in the Kaplan-Meier survival curves (Figure 4). Treatment with dibromoacetic acid had no effect on survival of male or female mice.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of 50 and 500 mg/L male mice were greater than those of the controls after week 85 (Figure 5; Tables 17 and 18). Mean body weights of exposed groups of female mice were generally similar to those of the controls throughout the study. Water consumption by exposed mice was generally similar to that by controls throughout the study (Tables J3 and J4). Drinking water concentrations of 50, 500, and 1,000 mg/L resulted in average daily doses of approximately 4, 45, and 87 mg/kg to males and 4, 35, and 65 mg/kg to females.

TABLE 16
Survival of Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Animals initially in study	50	50	50	50
Other[a]	1	0	0	0
Moribund	4	6	3	6
Natural deaths	14	6	13	13
Animals surviving to study termination	31	38	34	31
Percent probability of survival at end of study[b]	63	76	68	62
Mean survival (days)[c]	685	703	689	690
Survival analysis[d]	P=0.428	P=0.221N	P=0.813N	P=1.000
Female				
Animals initially in study	50	50	50	50
Moribund	2	2	5	7
Natural deaths	10	13	13	11
Animals surviving to study termination	38	35	32[e]	32
Percent probability of survival at end of study	76	70	64	64
Mean survival (days)	704	700	695	697
Survival analysis	P=0.276	P=0.658	P=0.273	P=0.309

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A lower mortality in an exposed group is indicated by **N**.
[e] Includes one animal that died during the last week of the study

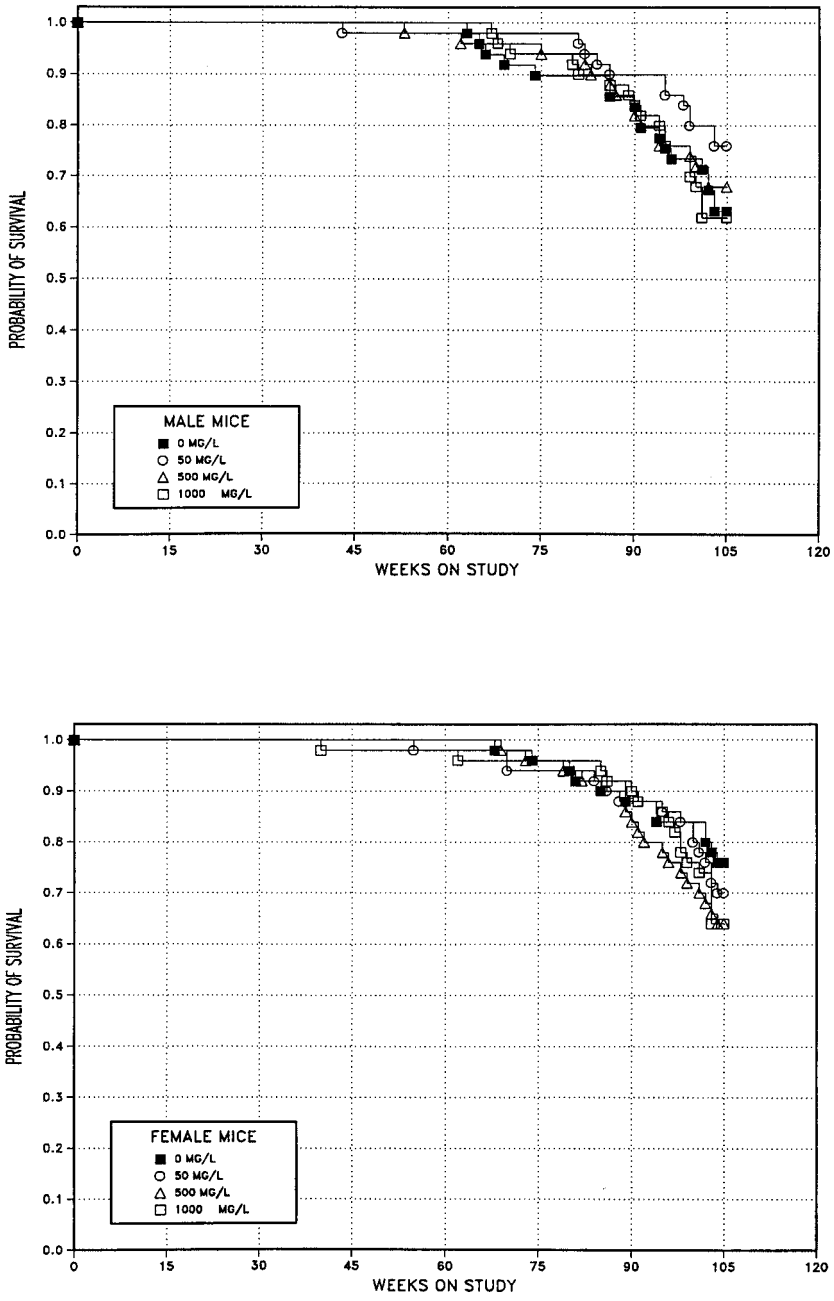
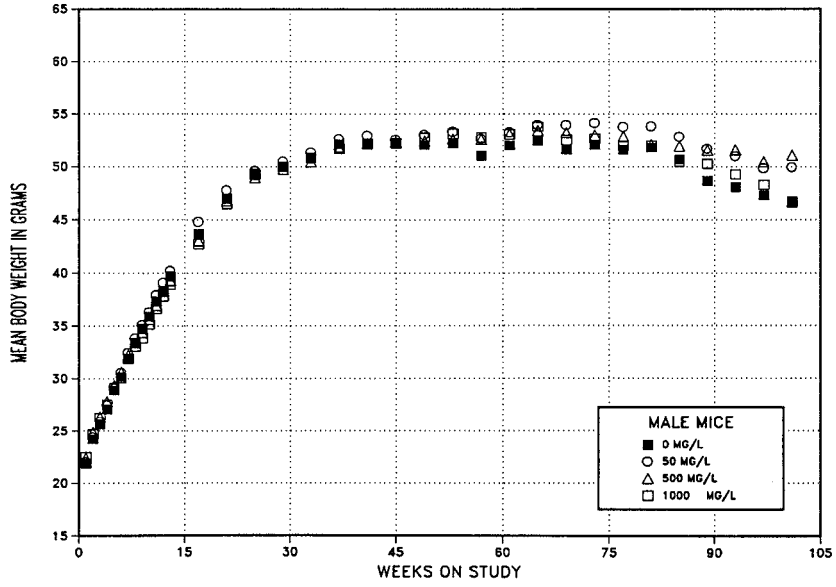


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Dibromoacetic Acid in Drinking Water for 2 Years



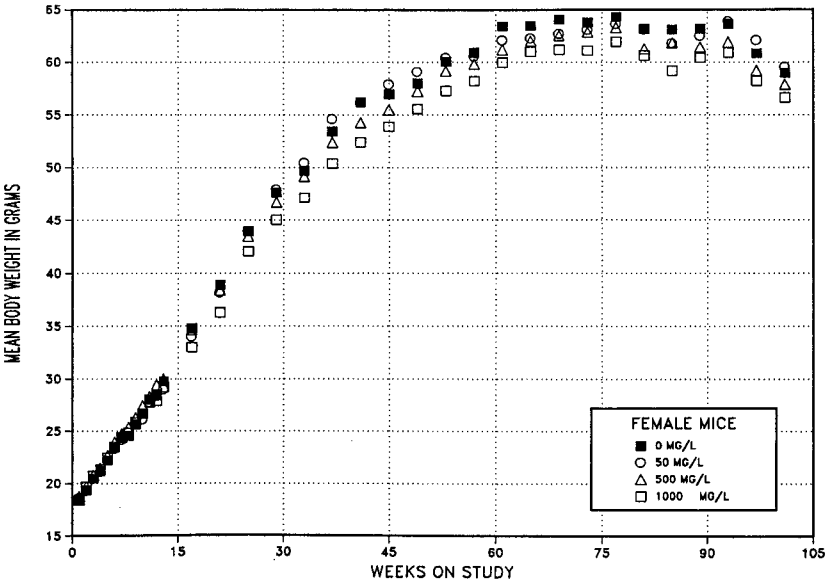


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Dibromoacetic Acid in Drinking Water for 2 Years

TABLE 17
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

Weeks on Study	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.9	50	22.1	101	50	22.4	102	50	22.5	103	50
2	24.2	50	24.4	101	50	24.9	103	50	24.7	102	50
3	25.7	50	25.9	101	50	26.3	102	50	26.2	102	50
4	27.1	50	27.4	101	50	27.8	103	50	27.5	102	50
5	28.9	50	29.2	101	50	29.3	101	50	29.1	101	50
6	30.2	50	30.6	101	50	30.6	101	50	30.1	100	50
7	31.9	50	32.4	102	50	32.2	101	50	31.9	100	50
8	33.4	50	33.8	101	50	33.4	100	50	33.1	99	50
9	34.8	50	35.1	101	50	34.4	99	50	33.9	97	50
10	35.9	50	36.3	101	50	35.6	99	50	35.2	98	50
11	37.4	50	37.9	101	50	36.9	99	50	36.6	98	50
12	38.3	50	39.1	102	50	38.3	100	50	37.8	99	50
13	39.7	50[a]	40.2	101	50	39.3	99	50	38.9	98	50
17	43.7	50	44.8	103	50	43.0	98	50	42.7	98	50
21	47.0	50	47.8	102	50	46.8	100	50	46.5	99	50
25	49.4	50	49.6	100	50	48.9	99	50	49.3	100	50
29	50.0	50	50.5	101	50	49.8	100	50	50.0	100	50
33	50.9	49	51.3	101	50	50.5	99	50	50.8	100	50
37	52.2	49	52.6	101	50	51.7	99	50	51.8	99	50
41	52.1	49	52.9	102	50	52.2	100	50	52.2	100	50
45	52.2	49	52.5	101	49	52.3	100	50	52.3	100	50
49	52.1	49	53.0	102	49	52.4	101	50	52.8	101	50
53	52.2	49	53.3	102	49	52.6	101	50	53.1	102	50
57	51.1	49	52.7	103	49	52.6	103	49	52.8	103	50
61	52.0	49	53.3	103	49	53.1	102	49	53.1	102	50
65	52.5	48	54.0	103	49	53.4	102	48	53.8	103	50
69	51.7	46	54.0	104	49	53.3	103	48	52.6	102	48
73	52.1	45	54.1	104	49	53.0	102	48	52.6	101	47
77	51.6	44	53.8	104	49	52.9	103	47	52.0	101	47
81	51.8	44	53.8	104	48	52.1	101	47	52.0	100	46
85	50.7	44	52.8	104	46	51.9	102	45	50.5	100	45
89	48.7	42	51.7	106	45	51.5	106	43	50.3	103	44
93	48.1	39	51.0	106	45	51.6	107	40	49.3	103	41
97	47.3	36	49.9	106	43	50.5	107	38	48.3	102	38
101	46.7	36	50.0	107	40	51.1	109	36	46.6	100	34
Mean for weeks											
1-13	31.5		31.9	101		31.6	101		31.3	100	
14-52	50.0		50.6	101		49.7	100		49.8	100	
53-101	50.5		52.6	104		52.3	104		51.4	102	

[a] Number of animals weighed for this week is less than the number surviving

TABLE 18
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

Weeks on Study	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.4	50	18.6	101	50	18.8	102	50	18.5	101	50
2	19.4	50	19.3	100	50	19.7	102	50	29.7	102	50
3	20.5	50	20.4	100	50	20.8	102	50	20.7	101	50
4	21.2	50	21.1	100	50	21.5	101	50	21.3	101	50
5	22.2	50	22.2	100	50	22.7	102	50	22.5	101	50
6	23.4	50	23.3	100	50	23.9	102	50	23.5	100	50
7	24.3	50	24.2	100	50	24.7	102	50	24.4	100	50
8	24.6	50	24.9	101	50	25.4	103	50	24.9	101	50
9	25.7	50	25.7	100	50	26.3	102	50	25.8	100	50
10	26.7	50	26.1	98	50	27.4	103	50	26.7	100	50
11	28.0	50	27.8	99	50	28.3	101	50	27.8	99	50
12	28.4	50	28.3	100	50	29.4	104	50	27.9	98	50
13	29.8	50	29.0	97	50	30.0	101	50	29.2	98	50
17	34.8	50	34.0	98	50	34.7	100	50	33.0	95	50
21	38.9	50	38.2	98	50	38.4	99	50	36.3	93	50
25	44.0	50	44.0	100	50	43.5	99	50	42.1	96	50
29	47.6	50	47.9	101	50	46.7	98	50	45.0	95	50
33	49.7	50	50.4	101	50	49.2	99	50	47.1	95	50
37	53.5	50	54.6	102	50	52.4	98	50	50.4	94	50
41	56.2	50	56.2	100	50	54.3	97	50	52.4	93	49
45	57.0	50	57.9	102	50	55.5	97	50	53.9	95	49
49	58.0	50	59.1	102	50	57.3	99	50	55.6	96	49
53	60.1	50	60.4	101	50	59.2	99	50	57.3	95	49
57	60.9	50	60.6	100	49	59.8	98	50	58.2	96	49
61	63.4	50	62.1	98	49	61.2	97	50	60.0	95	49
65	64.5	50	62.3	98	49	62.0	98	50	61.0	96	48
69	64.1	49	62.7	98	49	62.5	98	50	61.2	96	48
73	63.8	49	63.1	99	47	62.9	99	49	61.1	96	48
77	64.3	48	63.6	99	47	63.3	98	48	62.0	96	48
81	63.2	47	63.1	100	47	61.3	97	47	60.7	96	48
85	63.1	46	61.8	98	46	61.8	98	46	59.2	94	48
89	63.2	45	62.5	99	44	61.4	97	45	60.4	96	46
93	63.6	44	63.9	101	44	61.9	97	40	60.9	96	44
97	60.8	42	62.1	102	43	59.2	97	38	58.3	96	42
101	59.0	42	59.5	101	40	57.9	98	35	56.6	96	38
Mean for weeks											
1-13	24.0		23.9	100		24.5	102		24.1	100	
14-52	48.9		49.1	100		48.0	98		46.2	95	
53-101	62.5		62.1	99		61.1	98		59.8	96	

Toxicokinetics

In toxicokinetic studies similar to those conducted in rats, male and female B6C3F_1 mice were given a single gavage dose (70, 175, or 350 mg/kg) or a single intravenous injection (70 mg/kg) of dibromoacetic acid (Appendix N). The single gavage doses gave results that were described by the same model as in the rat study, with an elimination half-life range of approximately 2 to 7 minutes for males and females. The $AUC_{0\text{-}20\ minute}$ values increased with increasing dose, and the increase was greater than dose-proportional; this effect was attributed to a dose-dependent change in the terminal linear phase. Bioavailability increased with dose for both sexes of mice and ranged from approximately 11% to 44%.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of malignant lymphoma and neoplasms or nonneoplastic lesions of the liver, lung, eye, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The incidences of liver neoplasms occurred with positive trends in male and female mice (Tables 19, C3, and D3). The incidences of multiple hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in all exposed groups of males. The incidences of hepatoblastoma were significantly increased in 500 and 1,000 mg/L males, and the incidence of hepatocellular carcinoma was significantly increased in 1,000 mg/L males. The incidences of hepatocellular adenoma, carcinoma, and adenoma or carcinoma (combined) in all groups of males (except carcinoma at 50 mg/L) exceeded, or were at the high end of, the historical ranges in drinking water controls (Tables 19 and C4a). The incidence of hepatoblastoma in 1,000 mg/L males also exceeded the historical control range. The incidences of multiple hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in 500 and 1,000 mg/L females. The incidence of hepatocellular carcinoma was significantly increased in 500 mg/L females. The incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in 500 and 1,000 mg/L females exceeded the historical ranges in controls (Tables 19 and D4a).

Hepatocellular adenoma consisted of one or more discrete masses with distinct borders that caused definite compression of the surrounding normal parenchyma. Adenomas usually were composed of hepatocytes that appeared similar to the surrounding parenchyma except that the normal lobular architecture was not apparent and plates of neoplastic hepatocytes intersected the surrounding normal hepatocytes at sharp angles, rather than merging with them (Plates 7 and 8). Hepatocellular carcinoma consisted of one or more discrete masses that generally had irregular borders due to localized areas of growth of neoplastic hepatocytes into the surrounding normal parenchyma. The neoplastic hepatocytes often were somewhat atypical, but the major distinguishing feature of carcinoma was the presence of abnormal patterns of growth. The most common abnormal growth pattern was formation of trabeculae of neoplastic hepatocytes that were three or more cell layers thick, while less commonly the neoplastic cells formed glandular structures or solid masses (Plate 9).

Hepatoblastoma consisted of well-demarcated hypercellular areas, often with fluid- or blood-filled spaces and multifocal necrosis. The tumors were composed of pleomorphic collections of polygonal to elongated cells with ovoid to pyriform, hyperchromatic nuclei and variable amounts of eosinophilic to amphophilic cytoplasm. These cells were often arranged in palisading rows or glandular, "rosette" formations. Mitotic figures were numerous (Plate 10). Hepatoblastomas were frequently diagnosed in mice that also had hepatocellular adenoma or carcinoma. There was no consistent difference in the microscopic appearance of the liver neoplasm between the control and exposed groups. Hepatoblastomas are rare neoplasms with a low spontaneous incidence in mice (Harada *et al.*, 1999). They are considered part of the continuum in the development of hepatocellular neoplasms, are often observed within or adjacent to an existing hepatocellular adenoma or carcinoma, and are considered an undifferentiated variant of hepatocellular neoplasms. With chemicals that are hepatocarcinogens, there appears to be a positive association between increased incidences of hepatoblastoma and increased incidences of hepatocellular carcinoma in mice; the malignant potential of hepatoblastoma appears to be similar to that of hepatocellular carcinoma. In NTP 2-year studies, as many as 6 (mean incidence 1.5%)

TABLE 19
Incidences of Neoplasms of the Liver in Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Number Examined Microscopically	49	50	50	50
Hepatocellular Adenoma, Multiple[a]	6	17*	24*	27**
Hepatocellular Adenoma (includes multiple)[b]				
Overall rate[c]	18/49 (37%)	37/50 (74%)	37/50 (74%)	42/50 (84%)
Adjusted rate[d]	41.6%	78.0%	80.1%	88.7%
Terminal rate[e]	14/31 (45%)	31/38 (82%)	29/34 (85%)	29/31 (94%)
First incidence (days)	596	573	573	469
Poly-3 test[f]	P<0.001	P<0.001	P<0.001	P<0.001
Hepatocellular Carcinoma, Multiple	3	2	5	15**
Hepatocellular Carcinoma (includes multiple)[g]				
Overall rate	14/49 (29%)	9/50 (18%)	19/50 (38%)	26/50 (52%)
Adjusted rate	31.3%	19.4%	40.7%	54.9%
Terminal rate	6/31 (19%)	6/38 (16%)	10/34 (29%)	14/31 (45%)
First incidence (days)	451	659	573	476
Poly-3 test	P<0.001	P=0.141N	P=0.236	P=0.016
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	28/49 (57%)	41/50 (82%)	42/50 (84%)	47/50 (94%)
Adjusted rate	61.2%	85.8%	88.3%	96.0%
Terminal rate	17/31 (55%)	33/38 (87%)	30/34 (88%)	30/31 (97%)
First incidence (days)	451	573	573	469
Poly-3 test	P<0.001	P=0.004	P<0.001	P<0.001
Hepatoblastoma, Multiple	0	0	3	2
Hepatoblastoma (includes multiple)[i]				
Overall rate	0/49 (0%)	4/50 (8%)	6/50 (12%)	18/50 (36%)
Adjusted rate	0.0%	8.7%	13.3%	39.1%
Terminal rate	0/31 (0%)	3/38 (8%)	3/34 (9%)	9/31 (29%)
First incidence (days)	—[j]	717	573	469
Poly-3 test	P<0.001	P=0.072	P=0.019	P<0.001
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	28/49 (57%)	41/50 (82%)	43/50 (86%)	48/50 (96%)
Adjusted rate	61.2%	85.8%	90.4%	97.4%
Terminal rate	17/31 (55%)	33/38 (87%)	31/34 (91%)	30/31 (97%)
First incidence (days)	451	573	573	469
Poly-3 test	P<0.001	P=0.004	P<0.001	P<0.001

TABLE 19
Incidences of Neoplasms of the Liver in Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Female				
Number Examined Microscopically	49	50	50	49
Hepatocellular Adenoma, Multiple	11	14	23**	26**
Hepatocellular Adenoma (includes multiple)[k]				
Overall rate	19/49 (39%)	26/50 (52%)	32/50 (64%)	35/49 (71%)
Adjusted rate	41.4%	56.8%	69.7%	75.9%
Terminal rate	18/38 (47%)	22/35 (63%)	26/32 (81%)	28/32 (88%)
First incidence (days)	653	694	573	636
Poly-3 test	P<0.001	P=0.098	P=0.004	P<0.001
Hepatocellular Carcinoma, Multiple	1	1	5	3
Hepatocellular Carcinoma (includes multiple)[l]				
Overall rate	3/49 (6%)	3/50 (6%)	12/50 (24%)	8/49 (16%)
Adjusted rate	6.5%	6.6%	26.7%	17.7%
Terminal rate	1/38 (3%)	2/35 (6%)	9/32 (28%)	7/32 (22%)
First incidence (days)	658	694	617	671
Poly-3 test	P=0.019	P=0.659	P=0.009	P=0.094
Hepatocellular Adenoma or Carcinoma[m]				
Overall rate	22/49 (45%)	28/50 (56%)	37/50 (74%)	37/49 (76%)
Adjusted rate	47.6%	61.2%	79.5%	79.8%
Terminal rate	19/38 (50%)	24/35 (69%)	28/32 (88%)	29/32 (91%)
First incidence (days)	653	694	573	636
Poly-3 test	P<0.001	P=0.131	P<0.001	P<0.001
Hepatoblastoma	1	0	1	0

* Significantly different (P≤0.05) from the control group by the Poly-3 test
**P≤0.01
[a] Number of animals with lesion
[b] Historical incidence for 2-year drinking water studies with controls given the NTP-2000 diet (mean ± standard deviation): 84/197 (34.3% ± 22.3%), range 34%-63%
[c] Number of animals with neoplasm/number of animals with liver examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[g] Historical incidence: 57/197 (23.3% ± 15.5%), range 18%-42%
[h] Historical incidence: 122/197 (49.7% ± 31.1%), range 48%-85%
[i] Historical incidence: 11/197 (4.5% ± 6.2%), range 0%-13%
[j] Not applicable; no neoplasms in animal group
[k] Historical incidence: 93/248 (37.6% ± 18.0%), range 18%-61%
[l] Historical incidence: 28/248 (11.3% ± 9.1%), range 4%-26%
[m] Historical incidence: 110/248 (44.4% ± 18.1%), range 20%-63%

hepatoblastomas have occurred in individual male control groups (all routes) fed the NTP-2000 diet; the highest control incidence was observed in a drinking water control group.

Lung: The incidences of alveolar/bronchiolar adenoma occurred with a positive trend in males and females (Tables 20, C3, and D3). The incidence of adenoma in 500 mg/L male mice was significantly greater than that in controls. Alveolar/bronchiolar carcinoma occurred in control and exposed mice. The incidences of alveolar/bronchiolar adenoma in 500 and 1,000 mg/L males exceeded the historical range in drinking water controls, and that of 1,000 mg/L females was at the upper end of the historical control range (Tables 20, C4b, and D4b). Increases in the incidences of alveolar hyperplasia were noted in all treated groups of males, but the increases were not significant. Alveolar/bronchiolar adenoma consisted of well demarcated hypercellular masses distorting the normal septal architecture and were characterized by well-differentiated cuboidal to round cells forming papillary projections into the alveolar or bronchiolar lumens and slight compression of the surrounding parenchyma. Alveolar/bronchiolar carcinoma consisted of more irregular hypercellular masses distorting the normal septal architecture and were characterized by fairly pleomorphic, polygonal to columnar cells forming papillary and solid projections into alveolar or bronchiolar lumens, with variable peripheral compression and invasion. There was no consistent difference in the microscopic appearance of the lung neoplasms between the control and treated groups.

Malignant lymphoma: A significant increase in the incidence of malignant lymphoma occurred in 50 mg/L male mice compared to controls (0 mg/L, 0/50; 50 mg/L, 5/50; 500 mg/L, 3/50; 1,000 mg/L, 2/50; Table C3), and the incidence exceeded the historical control range [5/199 (2.0% ± 2.5%), range 0%- 6%]. However there was a negative trend in the incidences of malignant lymphoma in the female mice, and the incidence in the 1,000 mg/L group was significantly decreased (27/50, 24/50, 17/50, 14/50; Table D3). In females, the incidences in the control and 50 mg/L groups were near the upper end of the historical control range while the incidence in the 1,000 mg/L group was near the middle of the historical control range [91/250 (36.4 ± 22.7), range 10%-58%].

Eye: The incidence of cataract was significantly increased in 1,000 mg/L male mice (0/49, 1/50, 1/50, 6/50; Table C5). Cataract, unilateral or bilateral, consisted of one or more areas within the lens composed of swelling, degeneration and fragmentation of the lens fibers. These were most often located just under the lens capsule. Because the eye was not routinely checked in NTP studies until recently, the real historical mean for this cataract is unknown. However, according to Geiss and Yoshitomi (1999), severe mature cataracts are uncommon in old $B6C3F_1$ mice; focal posterior subcapsular degeneration is more frequent (up to 15%). It is therefore suggested that the apparent increased incidence of cataracts in the present study is not treatment-related.

Spleen: The incidence of hematopoietic cell proliferation was significantly increased in male mice exposed to 1,000 mg/L (0 mg/L, 18/49; 50 mg/L, 20/50; 500 mg/L, 28/50; 1,000 mg/L, 38/50; Table C5). Hematopoietic cell proliferation consisted of an increase in the normal active hematopoietic tissue, expanding the red pulp. Both myeloid and erythroid cell series were affected; megakaryocytes were often increased as well.

TABLE 20
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Male				
Number Examined Microscopically	49	50	50	50
Alveolar Epithelium, Hyperplasia[a]	2 (1.5)[b]	6 (1.7)	6 (2.3)	7 (1.9)
Alveolar/bronchiolar Adenoma, Multiple	0	1	2	4
Alveolar/bronchiolar Adenoma (includes multiple)[c]				
Overall rate[d]	7/49 (14%)	5/50 (10%)	17/50 (34%)	12/50 (24%)
Adjusted rate[e]	16.3%	10.8%	38.4%	26.6%
Terminal rate[f]	5/31 (16%)	4/38 (11%)	15/34 (44%)	8/31 (26%)
First incidence (days)	482	596	604	489
Poly-3 test[g]	P=0.019	P=0.326N	P=0.016	P=0.178
Alveolar/bronchiolar Carcinoma, Multiple	2	1	2	3
Alveolar/bronchiolar Carcinoma (includes multiple)[h]	5	8	8	7
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	12/49 (24%)	12/50 (24%)	22/50 (44%)	17/50 (34%)
Adjusted rate	27.7%	25.7%	49.4%	37.3%
Terminal rate	8/31 (26%)	9/38 (24%)	18/34 (53%)	11/31 (36%)
First incidence (days)	482	596	604	489
Poly-3 test	P=0.066	P=0.513N	P=0.027	P=0.226

TABLE 20
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Female				
Number Examined Microscopically	50	50	50	50
Alveolar/bronchiolar Adenoma[j]				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rate	2.2%	6.5%	6.7%	13.2%
Terminal rate	1/38 (3%)	2/35 (6%)	1/32 (3%)	4/32 (13%)
First incidence (days)	729 (T)	490	553	636
Poly-3 test	P=0.044	P=0.307	P=0.297	P=0.054
Alveolar/bronchiolar Carcinoma[k]	1	2	2	2
Alveolar/bronchiolar Adenoma or Carcinoma[l]				
Overall rate	2/50 (4%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	4.4%	10.8%	11.0%	15.4%
Terminal rate	2/38 (5%)	3/35 (9%)	2/32 (6%)	5/32 (16%)
First incidence (days)	729 (T)	490	553	636
Poly-3 test	P=0.095	P=0.219	P=0.210	P=0.076

(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation: 26/199 (10.5% ± 7.7%), range 6%-20%
[d] Number of animals with neoplasm/number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[h] Historical incidence: 16/199 (6.4% ± 3.9%), range 6%-10%
[i] Historical incidence: 41/199 (16.5% ± 10.7%), range 12%-26%
[j] Historical incidence: 13/250 (5.2% ± 4.2%), range 2%-12%
[k] Historical incidence: 5/250 (2.0% ± 1.4%), range 0%-4%
[l] Historical incidence: 16/250 (6.4% ± 3.9%), range 2%-12%

GENETIC TOXICOLOGY

Dibromoacetic acid, tested over a concentration range of 33 to 10,000 µg/plate, was mutagenic in *Salmonella typhimurium* strain TA100, with and without 30% rat or hamster liver metabolic activation enzymes (S9); no activity was detected in strain TA98, with or without rat or hamster liver S9 enzymes (Table E1). Increased frequencies of micronucleated normochromatic erythrocytes (NCEs) were observed in peripheral blood samples from male B6C3F$_1$ mice administered 125 to 2,000 mg dibromoacetic acid/L in drinking water for 3 months; no increases in NCEs were seen in female mice similarly exposed (Table E2). No evidence of bone marrow toxicity, as measured by the percentage of immature (polychromatic) erythrocytes among total erythrocytes, was observed in either male or female mice.

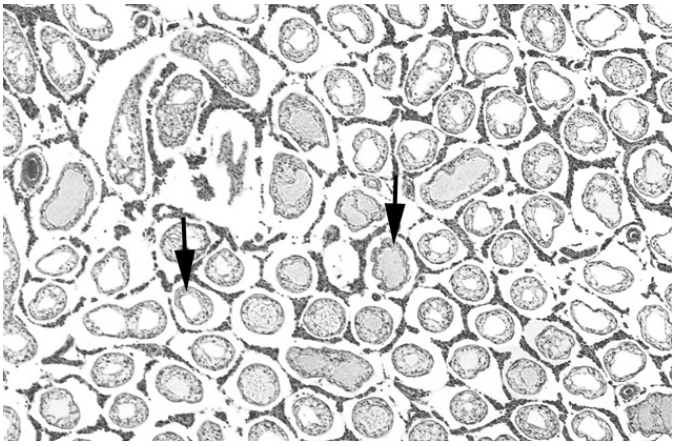


PLATE 1
Marked (grade 4) testicular atrophy (end stage lesion) in a male rat exposed to 2,000 mg/L dibromoacetic acid in drinking water for 3 months. Note that all seminiferous tubules (arrows) in the field are atrophic. H&E; 10×

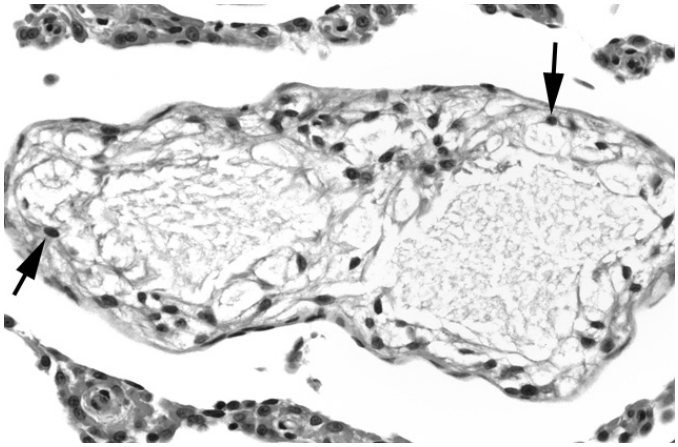


PLATE 2
Testicular atrophy (end stage lesion) in a male rat exposed to 2,000 mg/L dibromoacetic acid in drinking water for 3 months. The seminiferous tubules are lined only by Sertoli cells (arrows). H&E; 80×

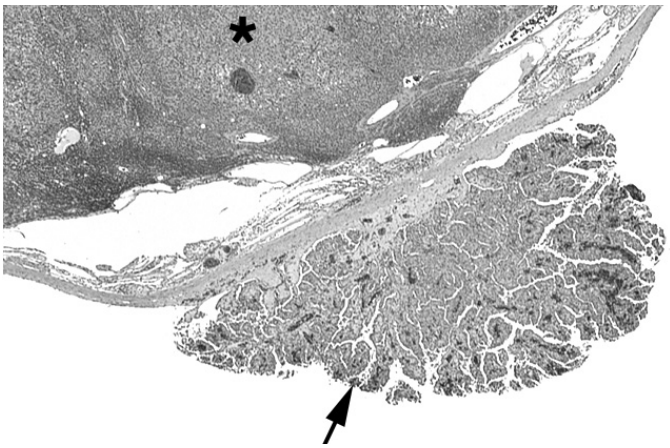


PLATE 3
Malignant mesothelioma (arrow) growing on the serosal surface of the testes in a male rat exposed to 1,000 mg/L dibromoacetic acid in drinking water for 2 years. There is also a spontaneous interstitial cell neoplasm (asterisk). H&E; 8×

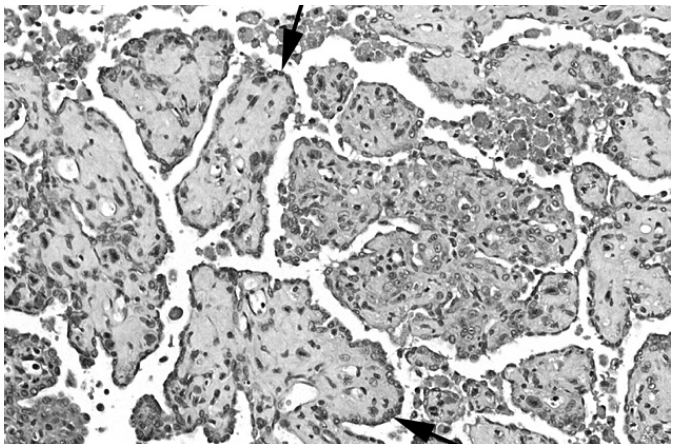


PLATE 4
Higher magnification of Plate 3 showing the structure of papillary exophytic projection (arrows) in the malignant mesothelioma. H&E; 50×

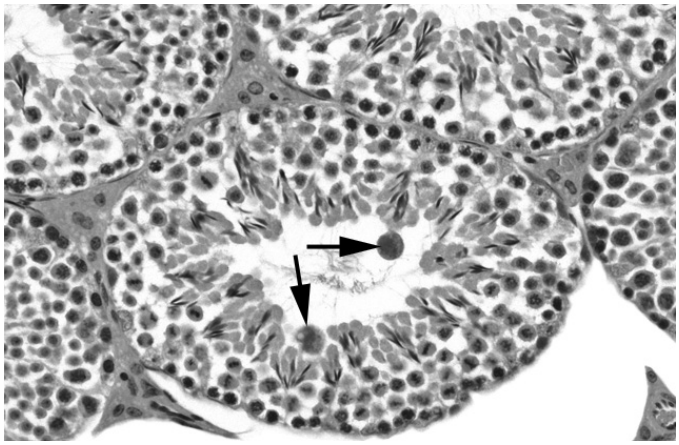


PLATE 5
Two abnormal residual bodies (arrows) in the testis of a male mouse exposed to 2,000 mg/L dibromoacetic acid in drinking water for 3 months. H&E; 80×

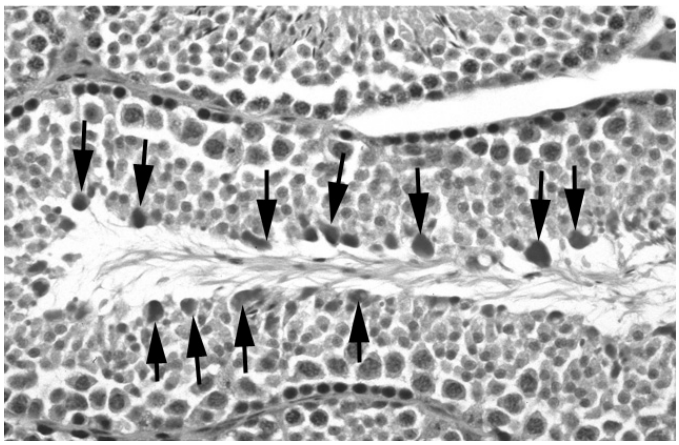


PLATE 6
Numerous abnormal residual bodies (arrows) in the testis of the same mouse presented in Plate 5. H&E; 80×

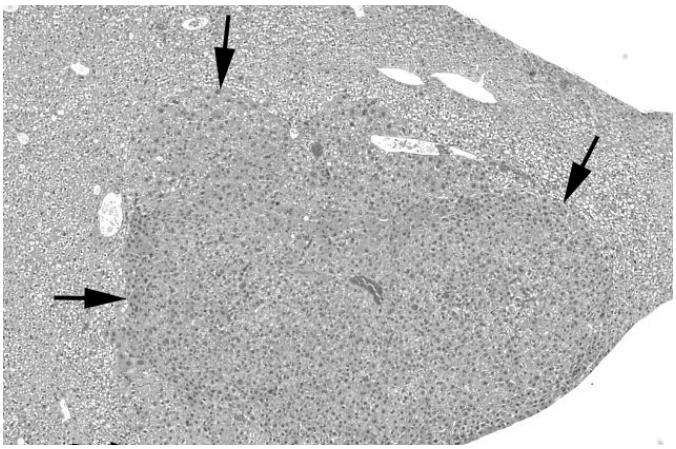


PLATE 7
Hepatocellular adenoma in a male mouse exposed to 1,000 mg/L dibromoacetic acid in drinking water for 2 years. The neoplasm had distinct borders, causing definite compression of the surrounding normal parenchyma (arrows). H&E; 10×

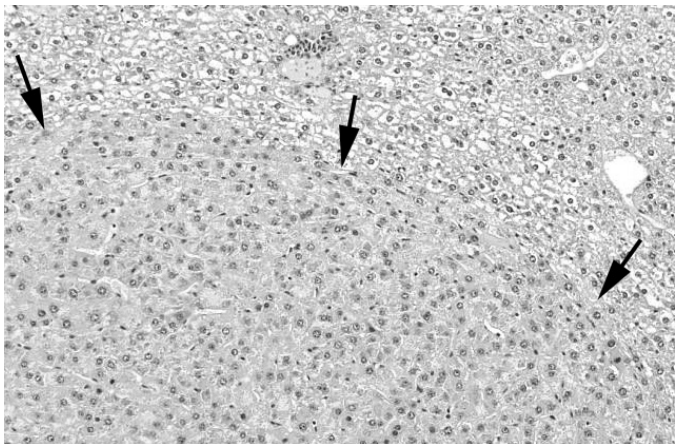


PLATE 8
Hepatocellular adenoma in a male mouse exposed to 1,000 mg/L dibromoacetic acid in drinking water for 2 years. Note the hepatocytes have a relatively normal appearance, the lack of normal lobular architecture, and the plates of neoplastic hepatocytes intersect the surrounding normal hepatocytes at sharp angles rather than merging with them (arrows). H&E; 20×

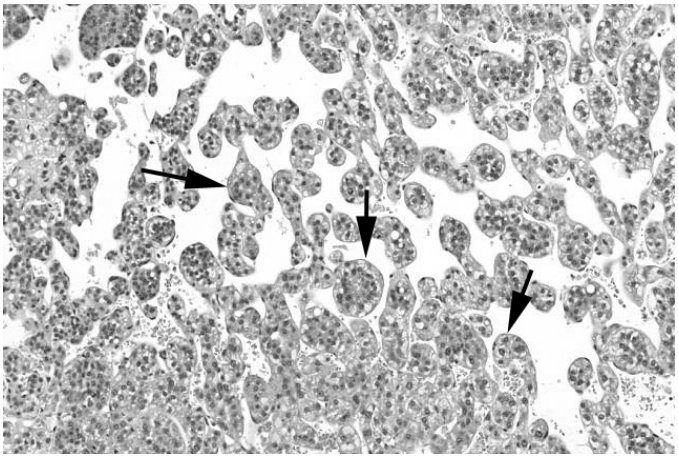


PLATE 9
Hepatocellular carcinoma in a male mouse exposed to 1,000 mg/L dibromoacetic acid in drinking water for 2 years. The neoplastic hepatocytes are somewhat atypical, with formation of trabeculae that are three or more cell layers thick (arrows). H&E; 10×

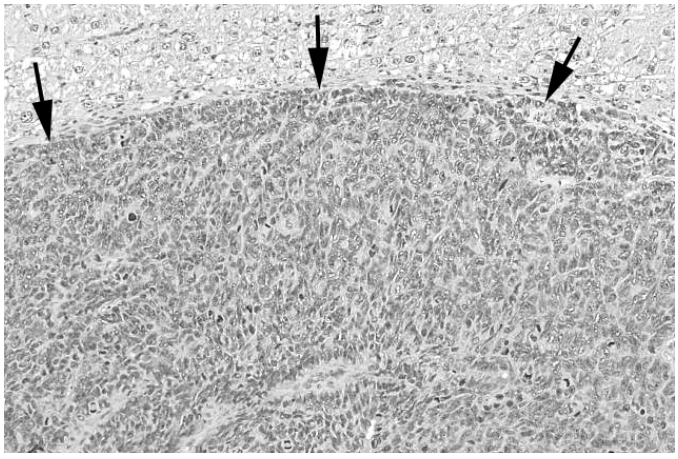


PLATE 10
Hepatoblastoma in a male mouse exposed to 1,000 mg/L dibromoacetic acid in drinking water for 2 years. The hypercellular neoplasm is well demarcated (arrows) and composed of a pleomorphic collection of polygonal to elongate cells with ovoid to pyriform, hyperchromatic nuclei. These cells are arranged in palisading rows or glandular, "rosette" formations. H&E; 10×

DISCUSSION AND CONCLUSIONS

Dibromoacetic acid is a drinking water disinfection by-product formed by the reaction of chlorine oxidizing agents with natural organic matter in source water containing bromide. The United States Environmental Protection Agency regulates drinking water levels of dibromoacetic acid, along with monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, and monobromoacetic acid at a limit of 60 µg/L for the sum of these haloacetic acids (40 CFR, § 141.64). Toxicity and carcinogenicity studies of dibromoacetic acid in rats and mice were nominated to the NTP by the USEPA because of widespread human exposure to this brominated water disinfection by-product and because a related dihaloacetic acid, dichloroacetic acid, was found to be carcinogenic to the liver of mice (Herren-Freund *et al.*, 1987; DeAngelo *et al.*, 1991; Daniel *et al.*, 1992) and rats (DeAngelo *et al.*, 1996). Dibromoacetic acid was administered in drinking water to mimic the major route of human exposure to this chemical.

In the 3-month drinking water study in rats, exposure to dibromoacetic acid (adjusted to pH 5.0) caused reductions in body weight gain in the 2,000 mg/L groups of males and females, increases in liver weights at all exposure concentrations (125 mg/L and higher), and minimal to mild hepatocellular cytoplasmic vacuolization at 500 mg/L or greater in males and in 2,000 mg/L females. The lowest exposure concentration in the 3-month study, 125 mg/L, resulted in an average daily dose of 10 mg dibromoacetic acid/kg body weight to males and 12 mg/kg to females. Hepatocyte cytoplasmic vacuolization in males exposed to 1,000 or 2,000 mg/L was associated with marginal increases in DNA replication, indicative of slight increases in hepatocyte proliferation. In a two-generation study, absolute and relative liver weights were increased in parental and F1 generation male and female Sprague-Dawley rats exposed to 50, 250, or 650 ppm (mg/L) dibromoacetic acid in drinking water; however, no corresponding microscopic changes in the liver were reported in that study (Christian *et al.*, 2002).

Testicular lesions induced in rats in 2-week and 3-month studies were similar to those described previously (Linder *et al.*, 1994b; 1997a) and were characterized by a delay in spermiation with retention of step 19 spermatids in the seminiferous epithelium adjacent to the lumen of stage IX and stage X tubules of the spermatogenic cycle. These changes were accompanied by the presence of atypical residual bodies. The lowest concentration of dibromoacetic acid showing this effect in the 3-month study was 500 mg/L, equivalent to a mean daily dose of 40 mg/kg. Decreased testicular weight and incidence of testicular atrophy were observed in the 2,000 mg/L group (166 mg/kg). Linder *et al.* (1997b) observed altered spermiation at 10 mg/kg or greater doses in Sprague-Dawley rats exposed to dibromoacetic acid by gavage for 31 or 79 days and seminiferous tubule atrophy at 250 mg/kg per day. The difference in dose response between the present study and that of Linder *et al.* (1997b) might be due to the use of different rat strains (F344/N versus Sprague-Dawley) or different methods of exposure (drinking water versus gavage). The formation of atypical residual bodies was suggested to be a result of impaired degradative function in Sertoli cells. Sperm morphology evaluations in the present study showed reductions in epididymal sperm counts, sperm motility, and spermatid heads at 2,000 mg/L (166 mg/kg) but not at 1,000 mg/L (90 mg/kg). Hypospermia was also diagnosed in the epididymis of rats in the present study. Linder *et al.* (1994b) detected altered sperm morphology and reduced sperm motility with 14 daily gavage doses of 90 mg/kg.

Pituitary gland hypertrophy observed in 2,000 mg/L males in the 3-month study was considered to be secondary to testicular atrophy because a similar response occurs following orchiectomy (MacKenzie and Boorman, 1990). In female rats, an increase in the incidence of hematopoietic cell proliferation in the spleen, characterized by increases in myeloid and erythroid precursors, was associated with mild decreases in white blood cell and lymphocyte counts at week 14. Increases in kidney, heart, lung, and thymus weights were not associated with microscopic changes in these organs.

Based on decreased body weight gains, organ weight effects, and the severity of testicular lesions at

2,000 mg/L, drinking water concentrations of dibromoacetic acid selected for the 2-year study were 50, 500, or 1,000 mg/L. In the 2-year study, these exposure concentrations had no effect on survival of male or female rats, while body weights of the 500 and 1,000 mg/L groups were at most 5% to 15% less than those of controls. These body weight differences were in part due to decreased water consumption and reduced feed intake.

An increase in the incidence of mesotheliomas was observed in the 1,000 mg/L group of male rats. The incidence of 20% in this group far exceeded the historical control rate of mesotheliomas in 2-year drinking water studies in male rats (mean incidence of 6% ± 4%). This malignant lesion was observed at multiple sites throughout the abdominal cavity (peritoneum). This response was consistent with the criteria for *some evidence of carcinogenic activity* in male rats. Chemically induced mesotheliomas have been observed predominantly in male rats compared to female rats or mice of either sex. Of over 500 carcinogenicity studies reported by the NTP, 16 agents produced positive evidence of neoplasms in the mesothelium; of those agents, 15 were active in male rats, two in female rats and mice, and one in male mice. Phenoxybenzamine was the only chemical that induced mesotheliomas in the abdominal cavity of both sexes of rats and mice (NCI, 1978). Both mutagenic and nonmutagenic chemicals induced neoplasms in the abdominal cavity mesothelium. There is no apparent relationship between chemical structure and this neoplastic response.

An increased incidence and positive trend for mononuclear cell leukemia was observed in female rats. The incidence in the high-dose (1,000 mg/L) female rats (44%) far exceeded the historical control rate for 2-year drinking water studies in which animals were given the NTP-2000 diet (mean incidence of 24% ± 4%). The incidence in the 1,000 mg/L female rats was also more than two standard deviations greater than the historical rate for 2-year feed studies in 510 female rats (mean incidence of 24% ± 9%). In male rats, the incidence of mononuclear cell leukemia was increased significantly in the low-dose (50 mg/L) group (62% versus 34% in controls), and a marginal increase was observed in the mid-dose (500 mg/L) group (48%). Both of these incidences exceeded the historical control rate for 2-year drinking water studies in which male rats were given NTP-2000 diet (mean incidence of 32% ± 3%). There was no difference in incidence of mononuclear cell leukemia between controls and high-dose (1,000 mg/L) males (26%). The mononuclear cell leukemia response in female rats was considered *some evidence of carcinogenic activity*, while the increased incidences in the low- and mid-dose groups of male rats may have been related to dibromoacetic acid exposure.

Several factors may influence the interpretation of mononuclear cell leukemia responses in male and female F344/N rats and evaluation of level of evidence of carcinogenicity for this neoplastic effect. Because the spontaneous rate of mononuclear cell leukemia in F344/N rats is high and variable, historical incidence data are extremely valuable for evaluating the response in a specific study. Table 21 provides survival and incidence data for mononuclear cell leukemia in male and female F344/N rats from NTP studies reported over the past 20 years in which evaluations of this neoplastic response were judged to be *equivocal evidence* (may have been related to chemical exposure) or *some evidence of carcinogenic activity*. In the dibromoacetic acid study, there was no effect of treatment on survival of male or female rats. Because it is difficult to estimate the expected incidences of mononuclear cell leukemia in some of the earlier NTP studies that had high mortality rates, the studies listed in Table 21 are limited to those in which survival rates in dosed groups were not significantly different from those in the respective concurrent control groups. It is important to note that historical rates have varied over this time period and that they are affected by diet and route of exposure. For example, in gavage studies with corn oil used as the vehicle for chemical administration, the incidence of mononuclear cell leukemia is decreased in control male rats but not in female rats compared to untreated controls (Haseman and Rao, 1992).

Dibromoacetic acid is one of four chemicals included in Table 21 that was administered in drinking water. In the other drinking water studies (pyridine, chlorinated water, and chloraminated water), animals were given the NIH-07 diet, and the level of evidence of carcinogenicity was judged to be *equivocal* in female rats (NTP, 1992, 2000a). In contrast to the results with dibromoacetic acid, for each of these three chemicals, there was *no evidence* of mononuclear cell leukemia in male rats, the increases in treated groups were within two standard deviations of the historical rates, and the incidences in the concurrent controls were 7% to 10% less than the historical rates that were used to evaluate responses in those studies. In fact, part of the rationale for the determination of *equivocal evidence of carcinogenicity* in those three studies was the lack of evidence for an increase in mononuclear cell leukemia in male rats and

TABLE 21
Incidence of Mononuclear Cell Leukemia in Male and Female F344/N Rats in Selected NTP Studies[a]

	Control	Low-Dose	Mid-Dose	High-Dose
Male				
Drinking Water Studies				
Dibromoacetic acid (TR 537), *equivocal evidence*				
Overall incidence	34%	62%**	48%	26%
Terminal survival	68%	48%	60%	57%
Historical control rate 31.6% ± 3.3%				
Pyridine (TR 470), *no evidence*[b]				
Overall incidence	58%	64%	52%	54%
Terminal survival	50%	40%	50%	32%
Chlorinated water (TR 392), *no evidence*[b]				
Overall incidence	49%	49%	54%	57%
Terminal survival	28%	12%	32%	33%
Chloraminated water (TR 392), *no evidence*[b]				
Overall incidence	49%	52%	57%	60%
Terminal survival	28%	44%	28%	32%
Gavage Study (Water)				
Hydroquinone (TR 366), *no evidence*[b]				
Overall incidence	51%	47%	NA[c]	56%
Terminal survival	51%	36%	NA	38%
Feed Studies				
o-Nitroanisole (TR 416), *some evidence*				
Overall incidence	52%**	50%	84%**	68%**
Terminal survival	64%**	69%	48%	18%**
Historical control rate 48.1% ± 7.7%				
Acetominophen (TR 394), *no evidence*[b]				
Overall incidence	54%	52%	48%	40%
Terminal survival	54%	56%	46%	48%
Gavage Studies (Corn Oil)				
Dichlorvos (TR 342), *some evidence*				
Overall incidence	22%**	40%*	NA	42%**
Terminal survival	63%	56%	NA	52%
Historical control rate 15.2% ± 8.8%				
Ampicillin trihydrate (TR 318), *equivocal evidence*				
Overall incidence	10%*	28%*	NA	26%*
Terminal survival	67%	54%	NA	55%
Historical control rate 14.0% ± 8.0%				
Inhalation Studies				
Indium phosphide (TR 499), *equivocal evidence*				
Overall incidence	32%	46%	58%*	50%
Terminal survival	54%	58%	58%	52%
Historical control rate 43.5% ± 9.6%				
Gallium arsenide (TR 492), *no evidence*				
Overall incidence	38%	56%	66%**	56%*
Terminal survival	26%	26%	30%	26%
Historical control rate 58.0% ± 8.0%				

TABLE 21
Incidence of Mononuclear Cell Leukemia in Male and Female F344/N Rats in Selected NTP Studies[a]

		Control	Low-Dose	Mid-Dose	High-Dose
Female					
Drinking Water Studies					
Dibromoacetic acid (TR 537), *some evidence*					
Overall incidence		22%**	26%	32%	44%*
Terminal survival		70%	78%	70%	64%
Historical control rate	23.5% ± 4.4%				
Pyridine (TR 470), *equivocal evidence*					
Overall incidence		24%*	32%	44%*	46%*
Terminal survival		64%	74%	58%	52%
Historical control rate	30.9% ± 10.0%				
Chlorinated water (TR 392), *equivocal evidence*					
Overall incidence		16%*	14%	37%*	32%
Terminal survival		62%	62%	55%	70%
Historical control rate	26.0% ± 8.5%				
Chloraminated water (TR 392), *equivocal evidence*					
Overall incidence		16%*	22%	30%	32%*
Terminal survival		62%	56%	58%	48%
Historical control rate	26.0% ± 8.5%				
Gavage Study (Water)					
Hydroquinone (TR 366), *some evidence*					
Overall incidence		16%**	27%*	NA	40%**
Terminal survival		73%	52%	NA	63%
Historical control rate	25.1% ± 14.9%				
Feed Studies					
o-Nitroanisole (TR 416), *some evidence*					
Overall incidence		28%**	22%	28%	52%*
Terminal survival		66%	83%	52%	65%
Historical control rate	26.6% ± 8.8%				
Acetominophen (TR 394), *equivocal evidence*					
Overall incidence		18%**	34%	30%	48%**
Terminal survival		60%	68%	68%	56%
Historical control rate	20.8% ± 8.1%				
Gavage Studies (Corn Oil)					
Dichlorvos (TR 342), *no evidence*[b]					
Overall incidence		34%	42%	NA	46%
Terminal survival		63%	52%	NA	52%
Ampicillin trihydrate (TR 318), *no evidence*					
Overall incidence		28%	36%	NA	26%
Terminal survival		64%	67%	NA	63%
Historical control rate	14.7% ± 8.3%				

TABLE 21
Incidence of Mononuclear Cell Leukemia in Male and Female F344/N Rats in Selected NTP Studies[a]

		Control	Low-Dose	Mid-Dose	High-Dose
Female (continued)					
Inhalation Studies					
Indium phosphide (TR 499), *equivocal evidence*					
Overall incidence		28%*	42%	28%	48%*
Terminal survival		68%	63%	72%	68%
Historical control rate	29.1% ± 8.5%				
Gallium arsenide (TR 492), *some evidence*					
Overall incidence		44%**	42%	36%	66%*
Terminal survival		38%	34%	42%	22%
Historical control rate	35.0% ± 5.9%				

* Significantly different ($P \leq 0.05$) from the control group by the life-table test or the Poly-3 test
**$P \leq 0.01$
[a] TR470, NTP, 2000a; TR392, NTP, 1992; TR366, NTP, 1989a; TR416, NTP, 1993a; TR394, NTP, 1993b; TR342, NTP, 1989b; TR318, NTP, 1987; TR499, NTP, 2001; TR492, NTP, 2000b
[b] Historical data not available
[c] NA=not applicable

the lower incidences of leukemia in the concurrent control groups of female rats compared to historical controls. In the dibromoacetic acid study, a significant increase in mononuclear cell leukemia was observed in low-dose males, and a marginal increase that exceeded the historical control range was observed in the mid-dose group. The higher spontaneous rates of mononuclear cell leukemia in control male F344/N rats fed the NIH-07 diet compared to the NTP-2000 diet might have masked the ability to detect an increased incidence of this neoplastic lesion in male rats exposed to pyridine, chlorinated water, or chloraminated water.

The increased incidence of mononuclear cell leukemia in female rats exposed to hydroquinone by gavage in water was judged to be *some evidence of carcinogenic activity* (NTP, 1989a). This response, which lacked supportive evidence in male rats, is not very different from that of dibromoacetic acid. In the two dosed-feed studies shown in Table 21, the mononuclear cell leukemia responses in female rats are similar to that of dibromoacetic acid. The effect of *o*-nitroanisole was considered to be *some evidence of carcinogenic activity* (NTP, 1993a), while the acetaminophen effects were considered to be *equivocal evidence of carcinogenicity* (NTP, 1993b). The latter determination was based on lack of supportive evidence in male rats, lack of evidence of shortened neoplasm latency in exposed groups, and the generally high and variable spontaneous rate of this neoplasm in F344/N rats.

Two corn oil gavage studies, dichlorvos (NTP, 1989b) and ampicillin trihydrate (NTP, 1987), are listed in Table 21. As noted above, this route of exposure is associated with decreased spontaneous rates of mononuclear cell leukemia in male rats. The mononuclear cell leukemia from the dichlorvos study in male F344/N rats was considered to be *some evidence of carcinogenic activity* in male rats. In each of these cases, there was no supportive evidence of mononuclear cell leukemia in female rats. The mononuclear cell leukemia for dibromoacetic acid in female rats is not very different from that of dichlorvos or ampicillin trihydrate in male rats.

In the two inhalation studies presented in Table 21, the increased incidences of mononuclear cell leukemia in female rats were judged to be *some evidence of carcinogenic activity* for gallium arsenide (NTP, 2000b) and *equivocal evidence of carcinogenic activity* for indium phosphide (NTP, 2001). Neither of these responses is very different from that of dibromoacetic acid, reflecting the difficulty in judging the appropriate level of evidence

for this neoplastic effect. The increased incidences of mononuclear cell leukemia in male rats exposed to gallium arsenide were not considered to be chemical-related because those rates were similar to the mean historical incidence in chamber control male rats.

The mononuclear cell leukemia response in female rats exposed to dibromoacetic acid included a positive trend and increased incidence that far exceeded historical rates for this neoplastic lesion; in addition, there were increased incidences of mononuclear cell leukemia in male rats. The response in female rats is generally consistent with previous NTP conclusions of *some evidence of carcinogenic activity*.

In female rats, the incidences of hyperplasia of the alveolar epithelium were significantly increased in the 500 and 1,000 mg/L groups; this response was accompanied by a marginal increase in the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) (4% in controls versus 10% in the 1,000 mg/L group). The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in this group of female rats exceeded the historical control rate for 2-year drinking water studies in which animals were given NTP-2000 diet (mean incidence of 4% ± 2%). Because alveolar epithelial hyperplasia is considered to be part of the continuum of proliferative lesions in lung neoplasia, the combined responses indicate a proliferative effect of dibromoacetic acid in the lung.

The only liver lesions observed in the 2-year study in rats were increased incidences of cystic degeneration in all exposed groups of males. This finding is in contrast to the increase in liver neoplasms observed in male F344/N rats exposed to 500 or 1,600 mg/L dichloroacetic acid in drinking water for 100 weeks (DeAngelo *et al*., 1996). On a molar basis, exposure to 500 mg/L dichloroacetic acid is equivalent to 845 mg/L dibromoacetic acid. Because there was no increase in the incidences of liver neoplasms in male rats given drinking water containing 1,000 mg/L dibromoacetic acid, there appears to be a difference in the hepatocarcinogenic potential of these two dihaloacetic acids in rats.

The incidences of chronic nephropathy were increased in all exposed groups of female rats but not in male rats; the apparent sex difference in identifying this renal effect is likely due to the higher rate of nephropathy in control male rats (88%) that precluded the chance of detecting an increased response. Increases in kidney weights were observed in male and female rats in the present 3-month study and in a two-generation drinking water study (Christian *et al.*, 2002), but no corresponding histopathological changes were noted in either of these studies. The present study indicates that exposure to dibromoacetic acid may exacerbate chronic nephropathy in rats.

In the 3-month drinking water study in mice, dibromoacetic acid caused reductions in body weight gain in the 2,000 mg/L groups of males and females and increases in liver weights at 500 mg/L or greater in both sexes. Although hepatocellular cytoplasmic vacuolization was observed in most mice including controls, the severity of this lesion was increased in the 1,000 and 2,000 mg/L groups. There was no increase in hepatocyte DNA replication in either sex of mice after 26 days of exposure.

Testicular lesions, similar to those observed in rats, were induced in mice exposed to 1,000 or 2,000 mg/L. These lesions, which had not been reported previously in mice, were characterized as spermatid retention and large atypical residual bodies in seminiferous tubules. The atypical residual bodies in mice were generally larger than those observed in rats (Plates 5 and 6); however, this effect was detected at a lower average daily dose in rats (40 mg/kg) than in mice (115 mg/kg). As noted above for rats, the lesions observed in mice were also probably caused by impaired degradative functions carried out by Sertoli cells. Evaluations of sperm from exposed mice did not demonstrate any effects on morphology, motility, or epididymal counts. Neither testicular atrophy nor decreases in testicular weight were observed in mice exposed to 2,000 mg/L, the concentration of dibromoacetic acid that caused these effects in rats.

Drinking water concentrations of dibromoacetic acid selected for the 2-year toxicology and carcinogenesis study (50, 500, and 1,000 mg/L) were based on decreased body weight gains and the severity of liver lesions at 2,000 mg/L. In the 2-year study, these exposure concentrations had no significant effects on survival, water consumption, or body weight gain in male and female mice.

Exposure of mice to dibromoacetic acid produced significant dose-related increases in the incidences of hepatocellular adenomas and carcinomas in males and females and hepatoblastomas in males. Of particular note is that the increase in hepatocellular neoplasms in male mice was significant even at the lowest exposure

concentration of 50 mg/L, which is equivalent to an average daily dose of approximately 4 mg/kg. Although the administration of dichloroacetic acid in drinking water for 2 years also induced hepatocellular neoplasms in male B6C3F$_1$ mice (DeAngelo *et al.*, 1991), significant increases in neoplasm incidence with dichloroacetic acid were not detected at doses as low as those of dibromoacetic acid that induced significant increases. The potent response observed in this study was not associated with hepatocellular necrosis or regenerative hyperplasia and was considered to be clear evidence of carcinogenic activity of dibromoacetic acid in male and female mice. A substantial species difference in susceptibility to dibromoacetic acid-induced liver neoplasia is noted by comparing the response in mice to the lack of a response in rats at equivalent exposure concentrations.

Dibromoacetic acid also induced a significant increase in the incidences of alveolar/bronchiolar neoplasms in male mice and a marginal increase in female mice. Also observed in male mice was a dose-related increase in the incidences of alveolar epithelial hyperplasia, a lesion that is considered to be part of the continuum of proliferative changes in lung neoplasia. Thus, the lung neoplastic response in male mice is considered to be related to dibromoacetic acid exposure, and the response in female mice may have been related to dibromoacetic acid exposure.

The 2-year studies presented here demonstrate the multiple organ carcinogenicity of dibromoacetic acid in laboratory animals; the primary sites identified in these studies include the abdominal cavity mesothelium of male rats and the liver and lung of mice. The mechanisms of neoplasm induction by dibromoacetic acid or the related dichloroacetic acid are not known. For dichloroacetic acid, it was suggested that the induction of liver tumors in mice is due to selective growth of a phenotypic cell-type that does not respond to mitoinhibitory homeostatic control mechanisms (Carter *et al.*, 2003). Neither hepatocellular necrosis nor regenerative hyperplasia was associated with the development of preneoplastic lesions or liver neoplasms in mice. A similar mechanism of liver neoplasm induction may be operating for dichloroacetic acid and dibromoacetic acid; data on dibromoacetic acid are not sufficient to ascertain any proposed hypothesis. DNA hypomethylation and increased expression of c-myc and IGF-II genes were suggested as possible early events in the hepatocarcinogenicity of dihaloacetic acids in mice (Pereira *et al.*, 2001; Tao *et al.*, 2004). An early increase in hepatocyte proliferation is not likely involved in the mode of action because no increases in the DNA labeling index were observed in mice exposed for 26 days and the slight increase that occurred in male F344/N rats was not accompanied by an increase in liver tumor response. DNA damage due to oxidative stress in the livers of mice exposed to halogenated acetic acids, including dibromoacetic acid (Austin *et al.*, 1996), may contribute to the hepatocarcinogenicity of these chemicals. The carcinogenicity of dibromoacetic acid may also involve a genotoxic mechanism because this agent induces DNA damage in *Escherichia coli* (Giller *et al.*, 1997), mutations in *Salmonella typhimurium* strains TA98 and TA100 with and without metabolic activation (Kargalioglu *et al.*, 2002), and DNA strand breaks in Chinese hamster ovary cells (Plewa *et al.*, 2002). In addition, glyoxylate, a metabolite of dihaloacetate biotransformation, is mutagenic in *S. typhimurium* strains TA97, TA100, and TA104 (Sayato *et al.*, 1987). It is possible that both a genotoxic effect and selective growth of an altered phenotypic cell-type are involved in the carcinogenesis of dibromoacetic acid. For example, increased cell replication rates in preneoplastic hepatic foci and tumors and decreased replication rates in normal hepatocytes of mice exposed to dibromoacetic acid would provide a selective growth advantage to initiated cells. DNA hypomethylation may contribute to the increased expression of proto-oncogenes during the development of liver neoplasms in mice exposed to dichloroacetic acid (Pereira *et al.*, 2001) or dibromoacetic acid (Tao *et al.*, 2004).

The various roles of parent compound and metabolites in the toxicity and carcinogenicity of dihaloacetic acids have not been determined. The major identified metabolites of dihaloacetate biotransformation in rats and mice are glyoxylate, glycolate, and oxalate (Lin *et al.*, 1993; Narayanan *et al.*, 1999). Biotransformation of dihaloacetates to glyoxylate occurs primarily in liver cytosol by a glutathione dependent process (James *et al.*, 1997) catalyzed by glutathione-*S*-transferase$_{zeta}$ (GSTζ) (Tong *et al.*, 1998a). However, because metabolism via the GSTζ-mediated displacement of a halide by glutathione leads to an irreversible inactivation of this enzyme (Anderson *et al.*, 1999), the rate of metabolic elimination is reduced and the internal dosimetry (or bioavailability) of the parent compound is increased with repeated exposures to dihaloacetic acids. This change in metabolic capability occurs until a new steady state level of GSTζ activity is reached; that level is dependent on the extent of inactivation and degradation of GSTζ in the

liver and the rate of resynthesis of this enzyme. Based on plasma-time course data for dibromoacetic acid in female rats and male mice, as well as published physiological and biochemical parameters, the absorption, metabolism, and elimination of this chemical in rats and mice plus the inactivation and resynthesis of GSTς in the liver were modeled (Appendix M). This physiologically based pharmacokinetic model (PBPK) was used to estimate the areas under each concentration versus time course curve (AUC) of dibromoacetate in the blood and liver, as well as the rate of metabolism of dibromoacetate in the liver via the GSTς pathway and a nonGSTς pathway in rats and mice receiving the drinking water concentrations used in the 2-year studies. In rats, the concentrations of dibromoacetate in the blood and liver increase disproportionately with increasing concentrations of dibromoacetic acid in the drinking water; for example, after 15 months of exposure, the blood AUC increased approximately 600-fold at the 500 mg/L concentration compared to 50 mg/L and increased another 6 fold at the 1,000 mg/L concentration (Figure 6). In contrast, the rate of metabolism of dibromoacetate via the GSTς pathway is equivalent at exposures of 500 and 1,000 mg/L. The nonlinear relationships between these various internal dose metrics and intake of dibromoacetic acid reflect the consequence of GSTς inactivation that occurs with dibromoacetate metabolism by this pathway. Because the shape of the dose response curve for mesotheliomas in male rats (neoplasm incidence versus exposure shown in Figure 7) appears to be similar to that of the blood AUC for dibromoacetate but very different from that of the GSTς metabolic activity, this neoplastic response may be due largely to parent compound.

In mice, the concentrations of dibromoacetate in the blood and liver and the rate of metabolism of dibromoacetate via the GSTς pathway increase proportionally with increasing concentrations of dibromoacetic

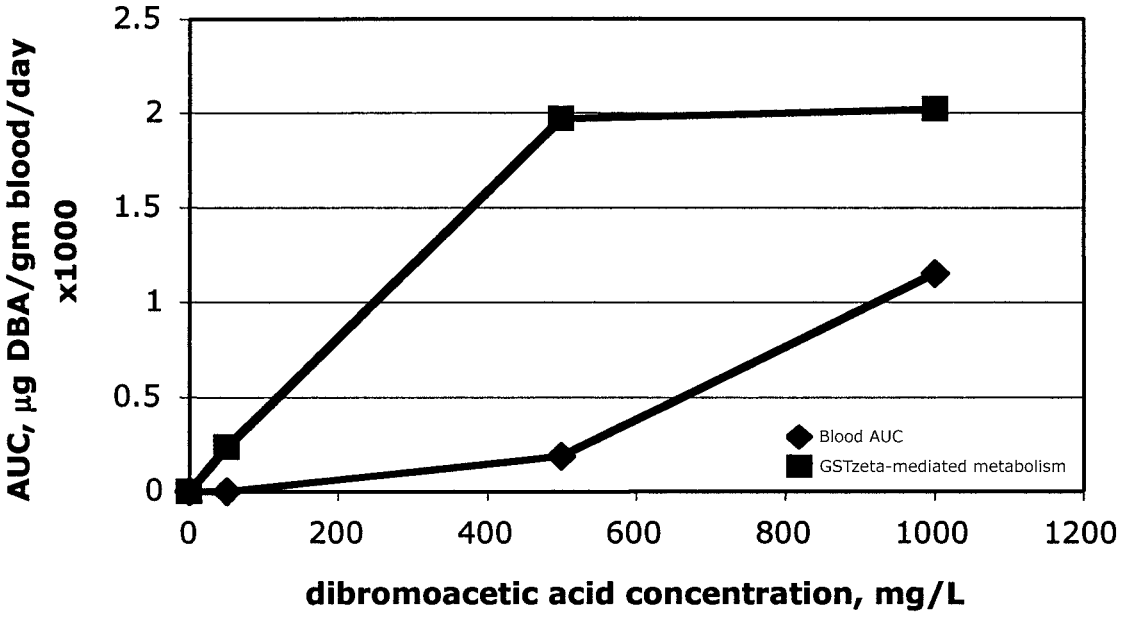


FIGURE 6
PBPK Model-Based Estimates of 24-Hour Blood AUCs for Dibromoacetate (DBA) and Daily Rates of GSTς-Mediated Metabolism in the Liver of Female F344/N Rats at 15 Months During the 2-Year Drinking Water Study of Dibromoacetic Acid

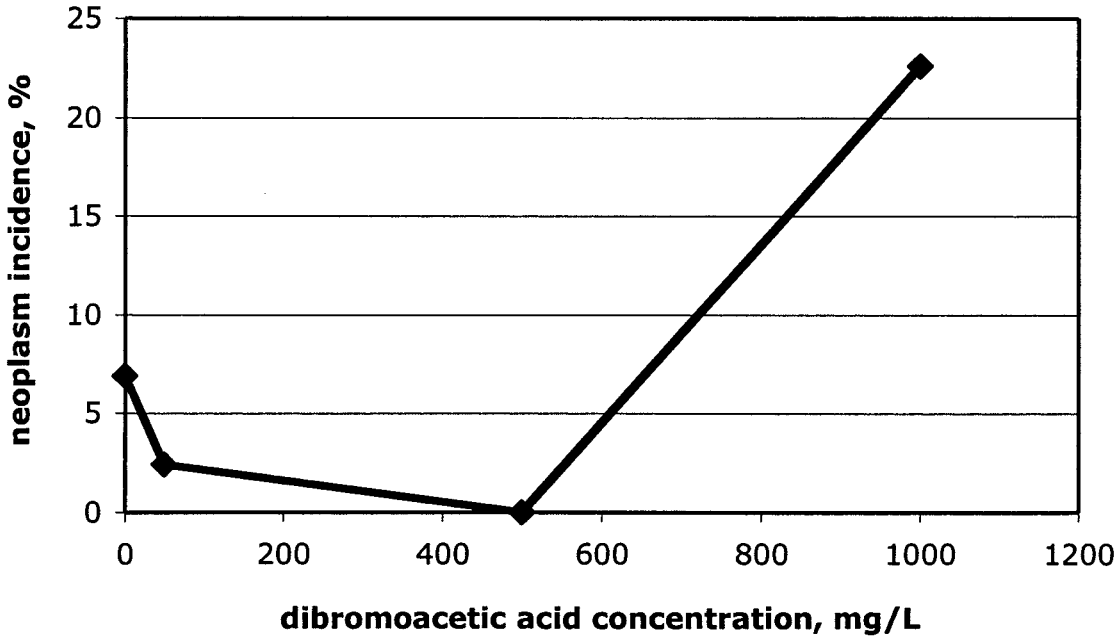


FIGURE 7
Survival-Adjusted (Poly-3) Mesothelioma Incidences in Male F344/N Rats Exposed to Dibromoacetic Acid in Drinking Water for 2 Years

acid in the drinking water (Figure 8). Similarly, the incidences of hepatoblastomas in male mice increase proportionally with increasing concentrations of dibromoacetic acid in the drinking water (Figure 9). Thus, the parent compound, metabolites, or both may be important contributors to this neoplastic response. The supralinear-appearing response for hepatocellular adenomas and carcinomas is different than the changes in parent compound concentration in the liver or the GSTς metabolic activity that occur with increasing concentrations of dibromoacetic acid in the drinking water. For example, at 50 mg/L of dibromoacetic acid, there were relatively low levels of dibromoacetate in the liver and low rates of GSTς-mediated metabolism, but there was a significant increase in hepatocellular neoplasms. Hence, it appears that the induction of hepatocellular neoplasms in mice may be very sensitive to low tissue levels of dibromoacetate or its metabolites.

The dose response for mononuclear cell leukemia in female rats is consistent with the exposure-related changes in GSTς-mediated metabolism and the blood levels of parent compound; however, the mononuclear cell leukemia response in male rats (increased incidence at 50 mg/L with no increase at 1,000 mg/L) is not consistent with the dose metrics derived from the PBPK model of dibromoacetic acid.

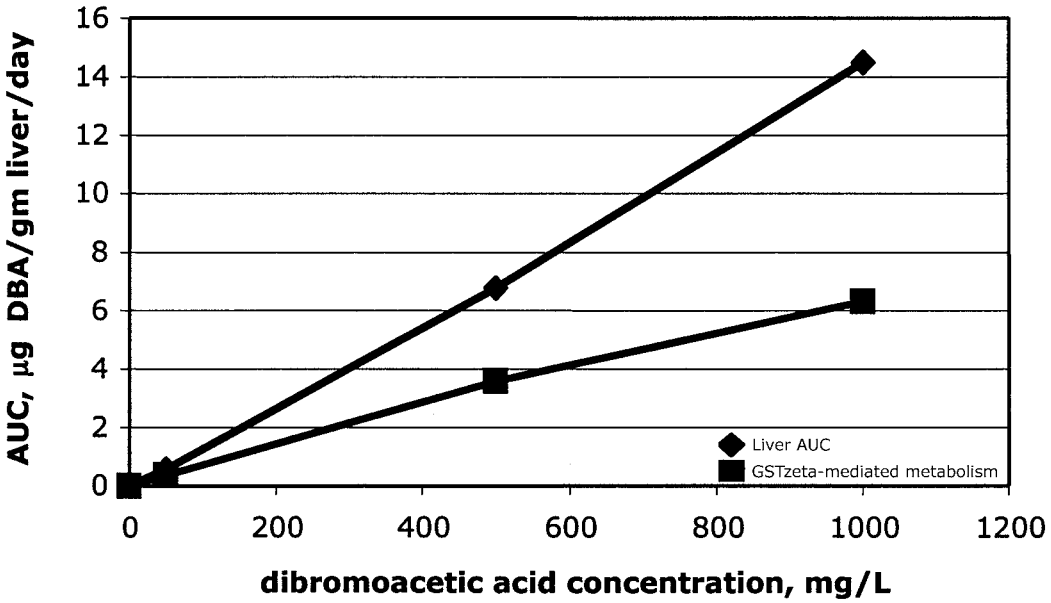


FIGURE 8
PBPK Model-Based Estimates of 24-Hour Liver AUCs for Dibromoacetate (DBA) and Daily Rates of GSTζ-Mediated Metabolism in the Liver of Male B6C3F$_1$ Mice at 15 Months During the 2-Year Drinking Water Study of Dibromoacetic Acid

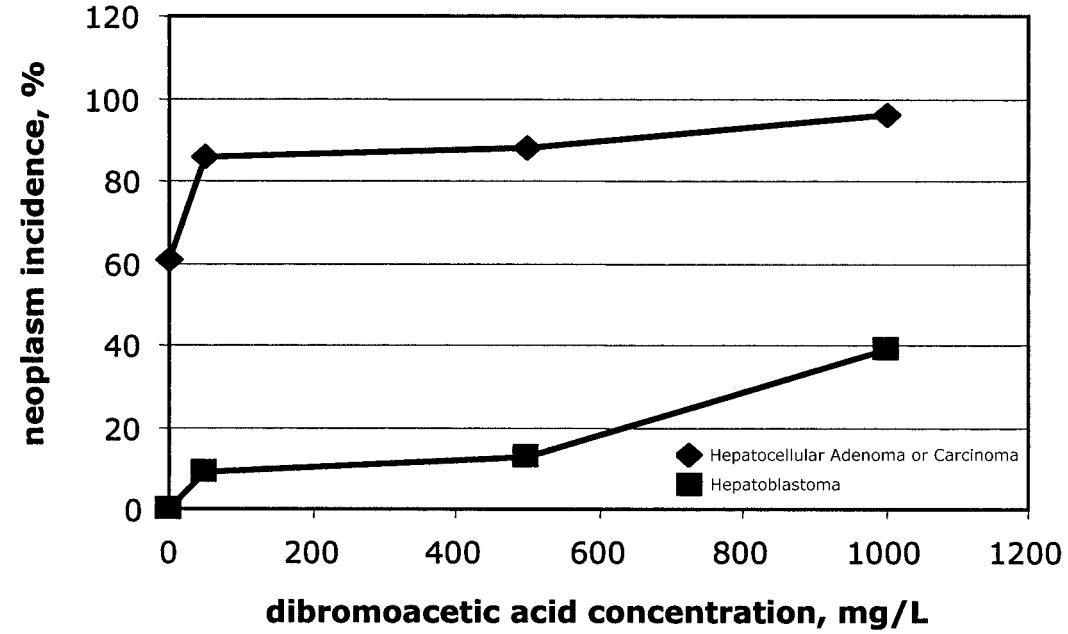


FIGURE 9
Survival-Adjusted (Poly-3) Liver Neoplasm Incidences in Male B6C3F$_1$ Mice Exposed to Dibromoacetic Acid in Drinking Water for 2 Years

CONCLUSIONS

Under the conditions of these studies, there was *some evidence of carcinogenic activity** of dibromoacetic acid in male rats based on an increased incidence of malignant mesothelioma. The increased incidences of mononuclear cell leukemia in male rats may have been related to dibromoacetic acid exposure. There was *some evidence of carcinogenic activity* of dibromoacetic acid in female rats based on an increased incidence and positive trend of mononuclear cell leukemia. There was *clear evidence of carcinogenic activity* of dibromoacetic acid in male and female mice based on increased incidences of hepatocellular neoplasms and hepatoblastoma (males only). Increased incidences of lung neoplasms in male mice were also considered to be exposure related. The slight increased incidence of lung neoplasms in female mice may have been related to dibromoacetic acid exposure.

Exposure to dibromoacetic acid for 2 years caused increased incidences of cystic degeneration of the liver in male rats, increased incidences of alveolar epithelial hyperplasia and nephropathy in female rats, and increased incidences of splenic hematopoiesis in male mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF DIBROMOACETIC ACID

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	4	15	12	12
Natural deaths	12	11	8	9
Survivors				
Died last week of study			3	
Terminal sacrifice	34	24	27	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(48)	(49)	(48)	(50)
Polyp adenomatous			1 (2%)	
Intestine large, cecum	(45)	(47)	(46)	(47)
Intestine small, duodenum	(45)	(48)	(47)	(48)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Mesentery	(10)	(14)	(11)	(17)
Fibrosarcoma, metastatic, skin			1 (9%)	
Histiocytic sarcoma	1 (10%)			
Rhabdomyosarcoma	1 (10%)			
Oral mucosa			(1)	
Pharyngeal, squamous cell carcinoma			1 (100%)	
Pancreas	(48)	(50)	(48)	(49)
Histiocytic sarcoma	1 (2%)			
Acinus, adenoma		2 (4%)	2 (4%)	1 (2%)
Salivary glands	(50)	(50)	(49)	(50)
Stomach, forestomach	(50)	(49)	(49)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		
Stomach, glandular	(50)	(48)	(48)	(50)
Tooth			(1)	
Odontoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Schwannoma malignant, metastatic, lung			1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(50)
Adenoma				1 (2%)
Histiocytic sarcoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Endocrine System (continued)								
Adrenal medulla	(49)		(50)		(49)		(50)	
Pheochromocytoma malignant			2	(4%)			1	(2%)
Pheochromocytoma complex							1	(2%)
Pheochromocytoma benign	7	(14%)	5	(10%)	7	(14%)	5	(10%)
Bilateral, pheochromocytoma benign			1	(2%)	1	(2%)	1	(2%)
Islets, pancreatic	(48)		(50)		(48)		(50)	
Adenoma	5	(10%)	3	(6%)	4	(8%)	1	(2%)
Carcinoma					1	(2%)		
Parathyroid gland	(50)		(50)		(48)		(47)	
Adenoma					1	(2%)		
Pituitary gland	(50)		(49)		(49)		(50)	
Pars distalis, adenoma	23	(46%)	21	(43%)	17	(35%)	8	(16%)
Pars intermedia, adenoma					1	(2%)		
Thyroid gland	(50)		(50)		(49)		(50)	
C-cell, adenoma	6	(12%)	5	(10%)	5	(10%)	7	(14%)
C-cell, carcinoma	1	(2%)	2	(4%)	1	(2%)	1	(2%)
Follicular cell, adenoma	1	(2%)			1	(2%)	2	(4%)
General Body System								
Peritoneum	(1)		(1)				(4)	
Schwannoma malignant, metastatic, peripheral nerve			1	(100%)				
Genital System								
Epididymis	(50)		(50)		(49)		(49)	
Preputial gland	(50)		(50)		(50)		(50)	
Adenoma	3	(6%)	5	(10%)	8	(16%)	4	(8%)
Squamous cell papilloma	1	(2%)						
Prostate	(50)		(50)		(50)		(50)	
Seminal vesicle	(50)		(50)		(49)		(50)	
Testes	(50)		(50)		(49)		(50)	
Bilateral, interstitial cell, adenoma	34	(68%)	42	(84%)	34	(69%)	39	(78%)
Interstitial cell, adenoma	7	(14%)	4	(8%)	7	(14%)	7	(14%)
Hematopoietic System								
Bone marrow	(49)		(49)		(48)		(50)	
Histiocytic sarcoma	1	(2%)						
Schwannoma malignant, metastatic, lung					1	(2%)		
Lymph node	(22)		(26)		(25)		(25)	
Bronchial, thymoma malignant, metastatic, thymus					1	(4%)		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1	(4%)				
Lymph node, mesenteric	(50)		(50)		(49)		(50)	
Hemangioma					1	(2%)		
Histiocytic sarcoma	1	(2%)						
Spleen	(50)		(50)		(49)		(49)	
Histiocytic sarcoma	1	(2%)						
Schwannoma malignant, metastatic, lung					1	(2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Hematopoietic System (continued)				
Thymus	(49)	(48)	(48)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Sarcoma	1 (2%)			
Thymoma benign	1 (2%)			
Thymoma malignant			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma	1 (2%)		1 (2%)	1 (2%)
Fibroadenoma	4 (8%)	5 (10%)	3 (6%)	5 (10%)
Fibroadenoma, multiple			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Keratoacanthoma	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Trichoepithelioma	1 (2%)	1 (2%)		
Sebaceous gland, adenoma, multiple				1 (2%)
Subcutaneous tissue, fibroma	5 (10%)	4 (8%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		3 (6%)	3 (6%)	2 (4%)
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, neural crest tumor	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, schwannoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Vertebra, chordoma		1 (2%)		
Skeletal muscle	(2)	(1)	(1)	(3)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)		
Hemangioma	1 (50%)			
Histiocytic sarcoma			1 (100%)	
Sarcoma	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Glioma malignant, mixed cell			1 (2%)	
Pineal gland, glioma malignant	1 (2%)			
Peripheral nerve	(2)	(1)	(2)	(2)
Schwannoma malignant		1 (100%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Respiratory System								
Lung	(50)		(50)		(50)		(50)	
Alveolar/bronchiolar adenoma	2	(4%)			4	(8%)	2	(4%)
Alveolar/bronchiolar carcinoma			1	(2%)	1	(2%)		
Carcinoma, metastatic, thyroid gland			1	(2%)				
Histiocytic sarcoma	2	(4%)			1	(2%)		
Schwannoma malignant, metastatic, eye			1	(2%)				
Schwannoma malignant, metastatic, heart					1	(2%)		
Squamous cell carcinoma					1	(2%)		
Mediastinum, sarcoma	1	(2%)						
Serosa, thymoma malignant, metastatic, thymus					1	(2%)		
Pleura	(1)				(1)			
Histiocytic sarcoma	1	(100%)						
Thymoma malignant, metastatic, thymus					1	(100%)		
Special Senses System								
Eye	(50)		(50)		(50)		(50)	
Schwannoma malignant			1	(2%)				
Harderian gland	(50)		(50)		(49)		(50)	
Zymbal's gland	(2)						(2)	
Adenoma	1	(50%)					1	(50%)
Carcinoma							1	(50%)
Urinary System								
Kidney	(49)		(50)		(49)		(50)	
Lipoma							1	(2%)
Renal tubule, adenoma	1	(2%)			1	(2%)		
Urinary bladder	(50)		(50)		(50)		(50)	
Carcinoma	1	(2%)						
Histiocytic sarcoma	1	(2%)						
Papilloma			1	(2%)				
Systemic Lesions								
Multiple organs[b]	(50)		(50)		(50)		(50)	
Histiocytic sarcoma	2	(4%)			1	(2%)		
Leukemia mononuclear	17	(34%)	31	(62%)	24	(48%)	13	(26%)
Lymphoma malignant lymphocytic							1	(2%)
Mesothelioma malignant	3	(6%)	1	(2%)			10	(20%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	49	50
Total primary neoplasms	145	146	147	127
Total animals with benign neoplasms	47	48	45	48
Total benign neoplasms	111	103	108	94
Total animals with malignant neoplasms	29	38	35	26
Total malignant neoplasms	33	43	39	33
Total animals with metastatic neoplasms		4	3	
Total metastatic neoplasms		7	8	
Total animals with uncertain neoplasms-benign or malignant	1			
Total uncertain neoplasms	1			

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 0 8	0 0 0 9	0 0 2 0	0 0 2 1	0 0 3 1	0 0 3 2	0 0 3 3	0 0 3 4	0 0 3 6	0 0 3 8	0 0 3 9	0 0 4 0	0 0 4 6	0 0 4 8	0 1 1 2	0 1 1 3	0 1 1 5	0 1 1 6	0 2 2 5	0 2 2 7	0 2 2 4	0 2 2 9	0 3 4 0	0 4 4 9	0 4 5 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																											1
Histiocytic sarcoma																											1
Mesentery		+					+	+								+						+					10
Histiocytic sarcoma								X																			1
Rhabdomyosarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma								X																			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																				X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																											1
Cardiovascular System																											
Blood vessel			+				+			+				+	+			+								+	13
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma								X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign	X			X									X					X			X						7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma									X		X		X														5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X						X	X	X	X	X						X			X	X			23
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X											X	X				X			X							6
C-cell, carcinoma										X																	1
Follicular cell, adenoma											X																1
General Body System																											
Peritoneum																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	2 2 2	4 3 3	4 3 7	5 1 6	5 3 0	5 9 1	6 1 6	6 2 2	6 2 9	6 2 9	6 6 1	6 8 2	6 9 2	6 9 3	7 0 3	7 1 1	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 3 5	0 2 2	0 3 7	0 2 3	0 2 6	0 1 7	0 1 4	0 1 6	0 1 0	0 1 4	0 4 2	0 4 7	0 1 9	0 1 8	0 2 8	0 4 1	0 1 1	0 1 3	0 4 4	0 4 5	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 7
Genital System																									
Coagulating gland													+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Squamous cell papilloma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X	X		X			X			X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma					X					X						X	X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Lymph node			+					+	+		+		+	+	+				+		+	+		+	
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Sarcoma	X																								
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X	
Fibroadenoma																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Histiocytic sarcoma																									
Keratoacanthoma																									
Squamous cell carcinoma																									
Squamous cell papilloma									X																
Trichoepithelioma																				X					
Subcutaneous tissue, fibroma				X	X						X														
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, neural crest tumor																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Hemangioma																									
Sarcoma	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 0 8	0 0 0 9	0 0 2 0	0 0 2 1	0 0 3 1	0 0 3 2	0 0 3 3	0 0 3 4	0 0 3 6	0 0 3 8	0 0 3 9	0 0 4 0	0 0 4 6	0 0 4 8	0 1 2	0 1 1 3	0 1 1 5	0 1 1 6	0 2 2 5	0 2 2 7	0 2 2 4	0 2 2 9	0 3 0	0 4 9	0 4 5 0	Total Tissues/ Tumors
Genital System																										
Coagulating gland										+				+				+								4
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X																								3
Squamous cell papilloma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	34
Interstitial cell, adenoma			X														X			X						7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node		+	+				+		+			+		+	+	+	+						+		+		22
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Histiocytic sarcoma																										1
Sarcoma																										1
Thymoma benign																					X					1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma							X						X										X			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma													X													1
Histiocytic sarcoma								X																		1
Keratoacanthoma		X	X					X																		3
Squamous cell carcinoma													X													1
Squamous cell papilloma																							X			2
Trichoepithelioma																										1
Subcutaneous tissue, fibroma															X				X							5
Subcutaneous tissue, hemangioma															X											1
Subcutaneous tissue, neural crest tumor			X																							1
Subcutaneous tissue, sarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle															+											2
Hemangioma															X											1
Sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	2 2 2	4 3 3	4 3 7	5 1 6	5 3 0	5 9 1	6 1 6	6 2 2	6 2 9	6 2 9	6 2 1	6 6 2	6 8 2	6 9 2	6 9 3	7 0 3	7 1 1	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 3 5	0 2 2	0 3 7	0 2 3	0 2 6	0 1 7	0 1 4	0 1 6	0 1 0	0 1 4	0 4 2	0 4 7	0 1 9	0 1 8	0 2 8	0 4 1	0 1 1	0 4 3	0 4 4	0 4 5	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 7
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pineal gland, glioma malignant		X																								
Peripheral nerve																									+	
Spinal cord																									+	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X							X						
Histiocytic sarcoma							X																			
Mediastinum, sarcoma	X																									
Nose	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura							+																			
Histiocytic sarcoma							X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																				X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																					
Histiocytic sarcoma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																			
Leukemia mononuclear			X	X				X	X		X			X					X	X	X	X		X		
Mesothelioma malignant						X												X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	730	730	730	733	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	733	734	734	734	734	
Carcass ID Number	00008	00009	00020	00021	00031	00032	00033	00034	00036	00038	00039	00040	00046	00048	00012	00013	00015	00016	00025	00027	00024	00029	00030	00049	00050	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pineal gland, glioma malignant																											1
Peripheral nerve					+																						2
Spinal cord					+																						2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																											2
Histiocytic sarcoma								X																			2
Mediastinum, sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pleura																											1
Histiocytic sarcoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																											
Ear														+													1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Zymbal's gland			+																	+							2
Adenoma			X																								1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Renal tubule, adenoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma																											1
Histiocytic sarcoma								X																			1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma								X																			2
Leukemia mononuclear	X								X						X	X	X								X		17
Mesothelioma malignant																X											3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	4 3 7	4 4 6	4 7 1	5 1 0	5 1 9	5 4 7	6 0 2	6 1 2	6 1 5	6 1 8	6 2 6	6 4 1	6 5 1	6 5 1	6 5 1	6 7 9	6 7 9	6 9 1	6 9 3	6 9 7	7 0 1	7 0 1	7 0 9	7 1 0	7 2 1
Carcass ID Number	0 6 5	1 0 0	0 8 2	0 9 5	0 8 4	0 6 8	0 5 7	0 9 1	0 9 2	0 9 0	0 6 2	0 5 8	0 5 1	0 6 7	0 9 4	0 6 6	0 7 3	0 8 7	0 5 6	0 8 5	0 7 1	0 7 8	0 7 9	0 5 5	0 9 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	A
Intestine small, ileum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery	+	+	+	+		+		+	+							+		+	+			+		+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma										X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Stomach, glandular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel										+	+		+				+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X																		X						
Pheochromocytoma benign										X									X			X		X	
Bilateral, pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X			X	X	X		X	X					X			X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X	X																					X
C-cell, carcinoma																									
General Body System																									
Peritoneum																									
Schwannoma malignant, metastatic, peripheral nerve																									
Genital System																									
Coagulating gland										+			+												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	724	729	729	729	729	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	734	734	
Carcass ID Number	07474	05440	06609	06611	06633	06644	07222	09233	08088	08899	09092	05252	05533	05599	06609	07700	07755	07766	07770	08080	08811	08833	08866	09077	09988	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X																							1
Mesentery		+																			+					14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma										X																2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel																			+				+			6
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Pheochromocytoma benign				X																						5
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																		X							3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X		X			X	X			X	X	X	X		X		X		X		X		21
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X																			X				5
C-cell, carcinoma	X												X													2
General Body System																										
Peritoneum																									+	1
Schwannoma malignant, metastatic, peripheral nerve																									X	1
Genital System																										
Coagulating gland																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	4 3 7	4 4 6	4 7 1	5 1 0	5 1 9	5 4 7	6 0 2	6 1 2	6 1 5	6 1 8	6 2 6	6 4 1	6 5 1	6 5 1	6 5 1	6 7 9	7 7 9	6 9 1	6 9 3	6 9 7	7 0 1	7 0 1	7 0 9	7 1 0	7 2 1
Carcass ID Number	0 6 5	1 0 0	0 8 2	0 9 5	0 8 4	0 6 8	0 5 7	0 9 1	0 9 2	0 9 0	0 6 2	0 5 8	0 5 1	0 6 7	0 9 4	0 6 6	0 7 3	0 8 7	0 5 6	0 5 8	0 7 1	0 7 8	0 7 9	0 5 5	0 9 6
Genital System (continued)																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X		X		X		X	X	X	X		X		X	X		X	X	X	X	X	X	X	X
Interstitial cell, adenoma												X		X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+		+	+	+	+			+	+	+		+				+	+	+	
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung															X										
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																					X		X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Squamous cell papilloma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma													X	X							X	X			
Subcutaneous tissue, fibrosarcoma										X			X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, chordoma																									X
Skeletal muscle															+										
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Schwannoma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	
Carcass ID Number	0 0 7 4	0 0 5 4	0 0 6 0	0 0 6 1	0 0 6 3	0 0 6 4	0 0 7 2	0 0 9 3	0 0 8 8	0 0 8 9	0 0 9 9	0 0 5 2	0 0 5 3	0 0 5 9	0 0 6 9	0 0 7 0	0 0 7 5	0 0 7 6	0 0 7 7	0 0 8 0	0 0 8 1	0 0 8 3	0 0 8 6	0 0 9 7	0 0 9 8	Total Tissues/ Tumors
Genital System (continued)																											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X		X								X			X										5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		42
Interstitial cell, adenoma																	X					X					4
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+			+							+	+						+	+	+	+	+	+			26
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma		X											X									X					5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																											1
Squamous cell papilloma				X																							1
Trichoepithelioma		X																									1
Subcutaneous tissue, fibroma																											4
Subcutaneous tissue, fibrosarcoma									X																		3
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, chordoma																											1
Skeletal muscle																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																									+		1
Schwannoma malignant																									X		1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	437	446	471	510	519	547	602	612	625	638	626	641	651	651	651	679	699	691	693	697	700	701	701	712
Carcass ID Number	06505	10600	08022	09905	08804	06608	05707	09901	09912	09900	06602	05408	05511	06617	09904	06663	07793	08537	05636	08565	07711	07718	07799	05955	09906
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																X									
Carcinoma, metastatic, thyroid gland																									
Schwannoma malignant, metastatic, eye																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear										+															
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																						X			
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																			X						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X	X	X		X	X				X			X	X	X		X		X	X	X	
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	
Carcass ID Number	0 0 7 4	0 0 5 4	0 0 6 0	0 0 6 1	0 0 6 3	0 0 6 4	0 0 7 2	0 0 9 3	0 0 8 8	0 0 8 9	0 0 9 9	0 0 5 2	0 0 5 3	0 0 5 9	0 0 6 9	0 0 7 0	0 0 7 5	0 0 7 6	0 0 7 7	0 0 8 0	0 0 8 1	0 0 8 3	0 0 8 6	0 0 8 7	0 0 9 8	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, thyroid gland													X													1
Schwannoma malignant, metastatic, eye																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X		X				X	X	X	X		X	X	X	X	X		X	X	X		31
Mesothelioma malignant														X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	0225	2253	4402	4423	4437	5521	5560	5660	5708	5800	5900	5904	6002	6007	6007	6008	6709	7000	7000	7001	7229	7299	7299	7299	7299
Carcass ID Number	1149	1207	1040	1009	1016	1225	1244	1445	1411	1015	1229	1237	1336	1160	1222	1228	1212	1117	1187	1201	1606	1199	1220	1226	1443
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Histiocytic sarcoma									X																
Mesentery				+			+						+		+	+		+	+	+		+			
Fibrosarcoma, metastatic, skin																						X			
Oral mucosa															+										
Pharyngeal, squamous cell carcinoma															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Tooth													+												
Odontoma													X												
Cardiovascular System																									
Blood vessel												+		+							+			+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, lung						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X											X	X						
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																	X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X		X						X	X			X	X			X	X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					
C-cell, carcinoma																							X		
Follicular cell, adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	734	734	
Carcass ID Number	14 48	12 23	12 24	13 30	13 31	13 32	13 33	13 34	13 35	13 39	14 00	14 01	14 42	14 42	10 21	10 02	10 03	11 33	11 14	11 15	11 38	14 46	14 47	15 05	10 07	10 08		Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Polyp adenomatous														X														1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma																X												1
Hepatocellular adenoma								X									X											2
Histiocytic sarcoma																												1
Mesentery								+										+										11
Fibrosarcoma, metastatic, skin																												1
Oral mucosa																												1
Pharyngeal, squamous cell carcinoma																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Acinus, adenoma		X						X																				2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Tooth																												1
Odontoma																												1
Cardiovascular System																												
Blood vessel																	+					+				+		7
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Schwannoma malignant, metastatic, lung																												1
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pheochromocytoma benign	X							X					X									X						7
Bilateral, pheochromocytoma benign						X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma		X																	X				X					4
Carcinoma																												1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		48
Adenoma																					X							1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma		X			X				X			X				X	X			X				X				17
Pars intermedia, adenoma																		X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell, adenoma	X		X				X											X										5
C-cell, carcinoma																												1
Follicular cell, adenoma							X																					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	0225	2253	4402	4423	4437	5521	5560	5660	5678	5780	5890	5904	6002	6007	6007	6008	6709	7000	7000	7001	7229	7229	7429	7429	7229
Carcass ID Number	1149	1207	1040	1009	1016	1025	1044	1045	1111	1055	1029	1237	1336	1160	1222	1228	1212	1117	1187	1201	1206	1199	1220	1226	1443
General Body System																									
None																									
Genital System																									
Coagulating gland														+										+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X	X		X		X		X		X				X	X		X	X	X	X
Interstitial cell, adenoma														X		X	X	X			X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, lung						X																			
Lymph node		+		+			+		+			A	+			+		+	+	+	+			+	+
Bronchial, thymoma malignant, metastatic, thymus		X																							
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, lung						X																			
Thymus	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X	
Fibroadenoma																									
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									X
Squamous cell papilloma																									X
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibrosarcoma			X																			X			
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Histiocytic sarcoma									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	734	
Carcass ID Number	14248	12233	12234	13300	13301	13312	13323	13334	13345	13359	14100	14401	14412	14201	00121	00232	01133	11144	11155	11158	13346	14467	14570	15070	10078	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Coagulating gland																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X						X		X			X						X	X					8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	34
Interstitial cell, adenoma			X														X									7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Schwannoma malignant, metastatic, lung																										1
Lymph node	+	+		+	+		+	+			+		+					+		+	+	+		+		25
Bronchial, thymoma malignant, metastatic, thymus																										1
Lymph node, mandibular	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	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																						X				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, lung																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma									X				X				X									3
Fibroadenoma, multiple	X																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell papilloma															X											2
Subcutaneous tissue, fibroma														X							X					3
Subcutaneous tissue, fibrosarcoma													X													3
Subcutaneous tissue, schwannoma malignant																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Histiocytic sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	0225	2253	4402	4233	4437	5521	5560	5660	5678	5780	5890	5990	6042	6007	6067	6068	6709	7000	7700	7701	7229	7299	7299	7299	7229
Carcass ID Number	14149	12027	10044	11009	11416	12125	12444	14455	11411	10155	12029	13377	13366	11102	12228	12282	11217	11177	11188	12021	10616	11199	12200	12266	14143
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant												X													
Glioma malignant, mixed cell																									
Peripheral nerve									+										+						
Spinal cord									+										+						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma									X																
Schwannoma malignant, metastatic, heart						X																			
Squamous cell carcinoma						X																			
Serosa, thymoma malignant, metastatic, thymus		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura		+																							
Thymoma malignant, metastatic, thymus		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Leukemia mononuclear				X			X					X		X	X			X	X	X		X		X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	14248	12323	12234	13300	13311	13323	13333	13343	13355	13359	14400	14411	14422	10121	10023	11033	11141	11155	13388	14466	14477	15070	10078	10088	Total Tissues/ Tumors
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																											1
Glioma malignant, mixed cell																				X							1
Peripheral nerve																											2
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X	X							X														4
Alveolar/bronchiolar carcinoma																	X										1
Histiocytic sarcoma																											1
Schwannoma malignant, metastatic, heart																											1
Squamous cell carcinoma																											1
Serosa, thymoma malignant, metastatic, thymus																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																											1
Thymoma malignant, metastatic, thymus																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma			X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Leukemia mononuclear	X			X	X		X	X			X		X			X		X			X	X		X	X		24

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	
Carcass ID Number	16303	16304	16305	16701	16811	16815	15757	15758	15759	16066	16772	16773	16774	16776	16779	19693	19694	19696	19698	15541	15512	15513	16888	19900	19902	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery		+					+					+		+					+				+	+		17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																											
Blood vessel						+					+		+							+						10
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma complex																							X			1
Pheochromocytoma benign					X				X																	5
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X																X				X	X	8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X							X		X							X	X			X		7
C-cell, carcinoma	X																									1
Follicular cell, adenoma	X																									2
General Body System																											
Peritoneum																										4
Genital System																											
Coagulating gland											+															3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X																								4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	3 5 6	3 8 6	4 2 3	5 1 2	5 1 4	5 2 1	5 6 1	5 7 0	5 7 1	6 1 0	6 1 8	6 2 4	6 3 1	6 3 3	6 4 4	6 5 1	6 5 1	6 5 1	6 7 4	6 7 9	7 0 1	7 2 3	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 8 3	1 7 0	1 8 2	1 8 4	1 9 1	1 7 5	1 9 7	1 7 7	1 7 8	1 6 9	1 8 0	1 8 7	1 9 9	1 8 9	1 5 4	1 5 5	1 6 7	1 9 5	1 6 8	2 0 0	1 8 6	1 1 6	1 5 6	1 6 0	1 6 2
Genital System (continued)																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		X		X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+					+	+	+	+	+		+	+	+	+	+		+	+	+	+	
Lymph node, mandibular	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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X							X		
Squamous cell papilloma																						X			
Sebaceous gland, adenoma, multiple														X											
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																				X					
Subcutaneous tissue, sarcoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
Skeletal muscle		+			+	+																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																								
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	16263	16264	16265	16271	16281	16285	16557	16558	16559	16566	16572	16573	16574	16576	16579	16593	16594	16596	16598	16611	16612	16613	16688	16690	16692	Total Tissues/ Tumors
Genital System (continued)																											
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		39
Interstitial cell, adenoma										X															X	7
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+					+	+						+				+		+			+	25
Lymph node, mandibular	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	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									X	1
Carcinoma														X												1
Fibroadenoma								X		X	X												X	X		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										2
Squamous cell papilloma				X																		X				3
Sebaceous gland, adenoma, multiple																										1
Subcutaneous tissue, fibroma																					X					1
Subcutaneous tissue, fibrosarcoma	X																									2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Skeletal muscle																										3
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																									+	2
Spinal cord																									+	2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																								X		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	3 5 6	3 8 6	4 2 3	5 1 2	5 1 4	5 2 1	5 6 1	5 7 0	5 7 1	6 1 0	6 1 8	6 2 4	6 3 1	6 3 3	6 4 4	6 5 1	6 5 1	6 5 1	6 7 4	6 7 9	7 0 1	7 2 3	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 8 3	1 7 0	1 8 2	1 8 4	1 9 1	1 7 5	1 9 7	1 7 7	1 7 8	1 6 9	1 8 0	1 8 7	1 9 9	1 8 9	1 5 4	1 5 5	1 6 7	1 9 5	1 6 8	2 0 0	1 8 6	1 1 6	1 5 6	1 6 0	1 6 2
Special Senses System																									
Ear																+									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland											+														
Zymbal's gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X								X			X		X		X	X			X	X			
Lymphoma malignant lymphocytic												X													
Mesothelioma malignant				X	X	X	X	X		X						X		X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	729	729	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	
Carcass ID Number	16303	16304	16305	16701	16801	16805	15057	15058	15059	16066	17072	17073	17074	17076	17079	19093	19094	19096	19098	15051	15052	15053	18880	19090	19092	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Zymbal's gland					+															+						2
Adenoma					X																					1
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X						X		X		X												13
Lymphoma malignant lymphocytic																										1
Mesothelioma malignant														X				X								10

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	7/49 (14%)	6/50 (12%)	8/49 (16%)	6/50 (12%)
Adjusted rate[b]	16.4%	14.2%	20.0%	14.5%
Terminal rate[c]	6/34 (18%)	1/24 (4%)	5/30 (17%)	3/28 (11%)
First incidence (days)	711	618	560	624
Poly-3 test[d]	P=0.549N	P=0.507N	P=0.445	P=0.523N
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	7/49 (14%)	7/50 (14%)	8/49 (16%)	8/50 (16%)
Adjusted rate	16.4%	16.3%	20.0%	19.2%
Terminal rate	6/34 (18%)	1/24 (4%)	5/30 (17%)	4/28 (14%)
First incidence (days)	711	437	560	624
Poly-3 test	P=0.371	P=0.607N	P=0.445	P=0.481
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.3%	2.4%	7.6%	2.5%
Terminal rate	1/34 (3%)	1/24 (4%)	3/30 (10%)	0/28 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	651
Poly-3 test	P=0.485	P=0.751	P=0.274	P=0.746
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.6%	0.0%	10.1%	4.9%
Terminal rate	1/34 (3%)	0/24 (0%)	4/30 (13%)	1/28 (4%)
First incidence (days)	682	—[e]	729 (T)	701
Poly-3 test	P=0.257	P=0.248N	P=0.295	P=0.668
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	2/50 (4%)
Adjusted rate	4.6%	2.4%	12.6%	4.9%
Terminal rate	1/34 (3%)	0/24 (0%)	5/30 (17%)	1/28 (4%)
First incidence (days)	682	651	729 (T)	701
Poly-3 test	P=0.331	P=0.515N	P=0.180	P=0.668
Mammary Gland: Fibroadenoma				
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rate	9.2%	12.0%	10.1%	12.4%
Terminal rate	4/34 (12%)	3/24 (13%)	4/30 (13%)	5/28 (18%)
First incidence (days)	729 (T)	701	729 (T)	729 (T)
Poly-3 test	P=0.447	P=0.474	P=0.595	P=0.455
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	4/50 (8%)	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted rate	9.2%	12.0%	10.1%	14.9%
Terminal rate	4/34 (12%)	3/24 (13%)	4/30 (13%)	6/28 (21%)
First incidence (days)	729 (T)	701	729 (T)	729 (T)
Poly-3 test	P=0.307	P=0.474	P=0.595	P=0.324
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	11.5%	12.0%	12.6%	17.4%
Terminal rate	5/34 (15%)	3/24 (13%)	5/30 (17%)	7/28 (25%)
First incidence (days)	729 (T)	701	729 (T)	729 (T)
Poly-3 test	P=0.249	P=0.605	P=0.575	P=0.328

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Pancreatic Islets: Adenoma				
Overall rate	5/48 (10%)	3/50 (6%)	4/48 (8%)	1/50 (2%)
Adjusted rate	11.9%	7.2%	10.2%	2.4%
Terminal rate	4/34 (12%)	1/24 (4%)	3/30 (10%)	0/28 (0%)
First incidence (days)	682	679	560	512
Poly-3 test	P=0.130N	P=0.363N	P=0.547N	P=0.107N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/48 (10%)	3/50 (6%)	5/48 (10%)	1/50 (2%)
Adjusted rate	11.9%	7.2%	12.7%	2.4%
Terminal rate	4/34 (12%)	1/24 (4%)	3/30 (10%)	0/28 (0%)
First incidence (days)	682	679	560	512
Poly-3 test	P=0.157N	P=0.363N	P=0.587	P=0.107N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	23/50 (46%)	21/49 (43%)	17/49 (35%)	8/50 (16%)
Adjusted rate	51.0%	48.9%	41.0%	19.3%
Terminal rate	16/34 (47%)	13/24 (54%)	11/30 (37%)	5/28 (18%)
First incidence (days)	591	602	560	512
Poly-3 test	P<0.001N	P=0.507N	P=0.232N	P<0.001N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	5/50 (10%)	8/50 (16%)	4/50 (8%)
Adjusted rate	6.9%	12.0%	20.1%	9.7%
Terminal rate	3/34 (9%)	4/24 (17%)	7/30 (23%)	2/28 (7%)
First incidence (days)	729 (T)	679	700	610
Poly-3 test	P=0.403	P=0.333	P=0.072	P=0.472
Skin: Squamous Cell Papilloma				
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.6%	2.4%	5.0%	7.4%
Terminal rate	1/34 (3%)	1/24 (4%)	2/30 (7%)	2/28 (7%)
First incidence (days)	629	729 (T)	729 (T)	723
Poly-3 test	P=0.244	P=0.519N	P=0.660	P=0.464
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.9%	2.4%	2.5%	4.9%
Terminal rate	3/34 (9%)	0/24 (0%)	1/30 (3%)	1/28 (4%)
First incidence (days)	729 (T)	693	729 (T)	651
Poly-3 test	P=0.548N	P=0.320N	P=0.337N	P=0.529N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	5/50 (10%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	11.4%	4.8%	5.0%	12.3%
Terminal rate	4/34 (12%)	1/24 (4%)	2/30 (7%)	3/28 (11%)
First incidence (days)	629	693	729 (T)	651
Poly-3 test	P=0.358	P=0.236N	P=0.256N	P=0.585

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	6/50 (12%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	13.7%	4.8%	5.0%	12.3%
Terminal rate	5/34 (15%)	1/24 (4%)	2/30 (7%)	3/28 (11%)
First incidence (days)	629	693	729 (T)	651
Poly-3 test	P=0.463	P=0.148N	P=0.165N	P=0.551N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	7/50 (14%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	16.0%	7.2%	5.0%	12.3%
Terminal rate	6/34 (18%)	2/24 (8%)	2/30 (7%)	3/28 (11%)
First incidence (days)	629	693	729 (T)	651
Poly-3 test	P=0.481N	P=0.177N	P=0.102N	P=0.430N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rate	11.2%	9.5%	7.5%	2.5%
Terminal rate	2/34 (6%)	0/24 (0%)	2/30 (7%)	1/28 (4%)
First incidence (days)	516	651	701	729 (T)
Poly-3 test	P=0.086N	P=0.538N	P=0.423N	P=0.127N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	7.1%	7.4%	4.9%
Terminal rate	0/34 (0%)	1/24 (4%)	2/30 (7%)	1/28 (4%)
First incidence (days)	—	618	402	679
Poly-3 test	P=0.357	P=0.113	P=0.107	P=0.222
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	2.3%	7.1%	7.4%	7.3%
Terminal rate	1/34 (3%)	1/24 (4%)	2/30 (7%)	1/28 (4%)
First incidence (days)	729 (T)	618	402	571
Poly-3 test	P=0.309	P=0.294	P=0.281	P=0.286
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
Adjusted rate	13.4%	14.1%	14.8%	9.7%
Terminal rate	3/34 (9%)	1/24 (4%)	4/30 (13%)	2/28 (7%)
First incidence (days)	516	618	402	571
Poly-3 test	P=0.346N	P=0.585	P=0.551	P=0.426N
Testes: Adenoma				
Overall rate	41/50 (82%)	46/50 (92%)	41/49 (84%)	46/50 (92%)
Adjusted rate	89.9%	95.8%	92.4%	96.6%
Terminal rate	33/34 (97%)	24/24 (100%)	28/30 (93%)	27/28 (96%)
First incidence (days)	530	437	437	423
Poly-3 test	P=0.228	P=0.194	P=0.475	P=0.149
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	5/50 (10%)	5/49 (10%)	7/50 (14%)
Adjusted rate	13.8%	11.7%	12.7%	17.4%
Terminal rate	6/34 (18%)	2/24 (8%)	4/30 (13%)	7/28 (25%)
First incidence (days)	729 (T)	471	701	729 (T)
Poly-3 test	P=0.314	P=0.508N	P=0.569N	P=0.444

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	7/50 (14%)	6/49 (12%)	8/50 (16%)
Adjusted rate	16.2%	16.3%	15.3%	19.8%
Terminal rate	7/34 (21%)	3/24 (13%)	5/30 (17%)	8/28 (29%)
First incidence (days)	729 (T)	471	701	729 (T)
Poly-3 test	P=0.378	P=0.606	P=0.576N	P=0.439
All Organs: Malignant Mesothelioma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	10/50 (20%)
Adjusted rate	6.9%	2.4%	0.0%	22.6%
Terminal rate	2/34 (6%)	1/24 (4%)	0/30 (0%)	2/28 (7%)
First incidence (days)	591	729 (T)	—	512
Poly-3 test	P<0.001	P=0.325N	P=0.137N	P=0.035
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	31/50 (62%)	24/50 (48%)	13/50 (26%)
Adjusted rate	37.0%	66.2%	56.2%	30.2%
Terminal rate	11/34 (32%)	15/24 (63%)	16/30 (53%)	5/28 (18%)
First incidence (days)	437	446	423	386
Poly-3 test	P=0.026N	P=0.003	P=0.051	P=0.325N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	48/50 (96%)	45/50 (90%)	48/50 (96%)
Adjusted rate	99.0%	97.6%	97.9%	99.5%
Terminal rate	34/34 (100%)	24/24 (100%)	30/30 (100%)	28/28 (100%)
First incidence (days)	516	437	437	423
Poly-3 test	P=0.456	P=0.630N	P=0.761N	P=0.987
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	38/50 (76%)	35/50 (70%)	26/50 (52%)
Adjusted rate	59.0%	78.4%	75.6%	53.9%
Terminal rate	18/34 (53%)	17/24 (71%)	21/30 (70%)	8/28 (29%)
First incidence (days)	222	437	253	356
Poly-3 test	P=0.084N	P=0.028	P=0.062	P=0.380N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	49/50 (98%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	34/34 (100%)	24/24 (100%)	30/30 (100%)	28/28 (100%)
First incidence (days)	222	437	253	356
Poly-3 test	P=1.000N	—[f]	P=1.000N	—

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Malignant Mesothelioma in Control Male F344/N Rats[a]

	Incidence in Controls
Historical Incidence: Drinking Water Studies	
Bromodichloromethane	3/50
Dibromoacetic acid	3/50
Dipropylene glycol	6/50
Sodium chlorate	0/50
Sodium nitrite	3/50
Overall Historical Incidence: Drinking Water Studies	
Total (%)	15/250 (6.0%)
Mean ± standard deviation	6.0% ± 4.2%
Range	0%-12%
Overall Historical Incidence	
Total (%)	57/1,459 (3.9%)
Mean ± standard deviation	3.9% ± 3.0%
Range	0%-12%

[a] Data as of January 26, 2005

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Control Male F344/N Rats[a]

	Incidence in Controls
Historical Incidence: Drinking Water Studies	
Bromodichloromethane	16/50
Dibromoacetic acid	17/50
Dipropylene glycol	16/50
Sodium chlorate	13/50
Sodium nitrite	17/50
Overall Historical Incidence: Drinking Water Studies	
Total (%)	79/250 (31.6%)
Mean ± standard deviation	31.6% ± 3.3%
Range	26%-34%
Overall Historical Incidence	
Total (%)	622/1,459 (42.6%)
Mean ± standard deviation	41.4% ± 12.3%
Range	22%-68%

[a] Data as of January 26, 2005; includes lymphocytic, monocytic, mononuclear, or undifferentiated leukemia

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Disposition Summary								
Animals initially in study	50		50		50		50	
Early deaths								
Accidental death							1	
Moribund sacrifice	4		15		12		12	
Natural death	12		11		8		9	
Survivors								
Died last week of study					3			
Terminal sacrifice	34		24		27		28	
Animals examined microscopically	50		50		50		50	
Alimentary System								
Intestine large, colon	(48)		(49)		(48)		(50)	
Edema			1	(2%)	1	(2%)		
Inflammation			1	(2%)				
Polyp, inflammatory							1	(2%)
Intestine large, cecum	(45)		(47)		(46)		(47)	
Congestion			1	(2%)				
Edema			1	(2%)				
Liver	(50)		(50)		(50)		(50)	
Basophilic focus	14	(28%)	4	(8%)	1	(2%)	1	(2%)
Cholangiofibrosis	1	(2%)						
Clear cell focus	18	(36%)	19	(38%)	16	(32%)	21	(42%)
Cyst	1	(2%)						
Degeneration, cystic	3	(6%)	9	(18%)	11	(22%)	15	(30%)
Eosinophilic focus	16	(32%)	4	(8%)	3	(6%)	9	(18%)
Hepatodiaphragmatic nodule	2	(4%)	1	(2%)	2	(4%)	5	(10%)
Inflammation, granulomatous	6	(12%)	1	(2%)			1	(2%)
Mixed cell focus	8	(16%)	1	(2%)	5	(10%)	2	(4%)
Necrosis, focal					3	(6%)	2	(4%)
Regeneration			1	(2%)	1	(2%)		
Bile duct, hyperplasia	43	(86%)	42	(84%)	35	(70%)	38	(76%)
Centrilobular, necrosis			1	(2%)	1	(2%)	5	(10%)
Hepatocyte, vacuolization cytoplasmic	14	(28%)	6	(12%)	12	(24%)	12	(24%)
Hepatocyte, midzonal, vacuolization cytoplasmic					1	(2%)		
Serosa, fibrosis	1	(2%)						
Serosa, inflammation	1	(2%)						
Mesentery	(10)		(14)		(11)		(17)	
Accessory spleen			1	(7%)	1	(9%)		
Fat, necrosis	8	(80%)	7	(50%)	7	(64%)	5	(29%)
Pancreas	(48)		(50)		(48)		(49)	
Atrophy	23	(48%)	28	(56%)	25	(52%)	23	(47%)
Cyst	1	(2%)	1	(2%)	1	(2%)		
Acinus, hyperplasia, focal	3	(6%)	5	(10%)	1	(2%)		
Salivary glands	(50)		(50)		(49)		(50)	
Inflammation, chronic					1	(2%)	1	(2%)

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Alimentary System (continued)								
Stomach, forestomach	(50)		(49)		(49)		(50)	
Edema	2	(4%)	5	(10%)	5	(10%)	2	(4%)
Erosion			4	(8%)	3	(6%)	1	(2%)
Ulcer	2	(4%)	5	(10%)	5	(10%)	3	(6%)
Epithelium, hyperplasia	7	(14%)	5	(10%)	5	(10%)	1	(2%)
Stomach, glandular	(50)		(48)		(48)		(50)	
Edema			5	(10%)	3	(6%)	1	(2%)
Erosion			6	(13%)	4	(8%)	1	(2%)
Hyperplasia, focal					1	(2%)		
Ulcer			3	(6%)	4	(8%)	2	(4%)
Tongue	(1)							
Hyperplasia	1	(100%)						
Cardiovascular System								
Heart	(50)		(50)		(50)		(50)	
Cardiomyopathy	45	(90%)	41	(82%)	43	(86%)	41	(82%)
Thrombosis			4	(8%)	1	(2%)	1	(2%)
Endocrine System								
Adrenal cortex	(49)		(50)		(49)		(50)	
Accessory adrenal cortical nodule	26	(53%)	18	(36%)	20	(41%)	14	(28%)
Degeneration, fatty	5	(10%)	12	(24%)	9	(18%)	4	(8%)
Hyperplasia, focal	6	(12%)	4	(8%)	2	(4%)	6	(12%)
Hypertrophy, focal	10	(20%)	12	(24%)	13	(27%)	8	(16%)
Necrosis			1	(2%)			1	(2%)
Adrenal medulla	(49)		(50)		(49)		(50)	
Hyperplasia	6	(12%)	8	(16%)	7	(14%)	8	(16%)
Necrosis			1	(2%)				
Islets, pancreatic	(48)		(50)		(48)		(50)	
Hyperplasia	1	(2%)			1	(2%)	1	(2%)
Pituitary gland	(50)		(49)		(49)		(50)	
Pars distalis, angiectasis	16	(32%)	14	(29%)	12	(27%)	9	(18%)
Pars distalis, cyst	1	(2%)	2	(4%)	5	(10%)	1	(2%)
Pars distalis, hemorrhage	1	(2%)	1	(2%)			1	(2%)
Pars distalis, hyperplasia							2	(4%)
Pars distalis, hyperplasia, focal	6	(12%)	10	(20%)	4	(8%)	3	(6%)
Pars intermedia, angiectasis					1	(2%)		
Pars intermedia, cyst			1	(2%)	2	(4%)		
Pars intermedia, hyperplasia					1	(2%)		
Thyroid gland	(50)		(50)		(49)		(50)	
Ultimobranchial cyst	5	(10%)			2	(4%)	3	(6%)
C-cell, hyperplasia	9	(18%)	13	(26%)	15	(31%)	4	(8%)
Follicle, cyst	4	(8%)	2	(4%)	2	(4%)	2	(4%)
General Body System								
None								

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Genital System								
Epididymis	(50)		(50)		(49)		(49)	
Inflammation, chronic	1	(2%)			1	(2%)	1	(2%)
Preputial gland	(50)		(50)		(50)		(50)	
Cyst	1	(2%)	6	(12%)	5	(10%)		
Hyperplasia			1	(2%)	1	(2%)		
Inflammation, chronic	1	(2%)	1	(2%)			3	(6%)
Prostate	(50)		(50)		(50)		(50)	
Inflammation, chronic	23	(46%)	25	(50%)	29	(58%)	29	(58%)
Seminal vesicle	(50)		(50)		(49)		(50)	
Inflammation					1	(2%)		
Testes	(50)		(50)		(49)		(50)	
Germinal epithelium, atrophy	11	(22%)	24	(48%)	13	(27%)	10	(20%)
Interstitial cell, hyperplasia	1	(2%)	5	(10%)	4	(8%)	4	(8%)
Hematopoietic System								
Bone marrow	(49)		(49)		(48)		(50)	
Depletion cellular							1	(2%)
Hyperplasia	2	(4%)	4	(8%)	2	(4%)	5	(10%)
Myelofibrosis					3	(6%)		
Lymph node	(22)		(26)		(25)		(25)	
Deep cervical, hyperplasia, lymphoid			1	(4%)				
Mediastinal, congestion	1	(5%)			1	(4%)	2	(8%)
Mediastinal, hyperplasia, lymphoid	8	(36%)	8	(31%)	13	(52%)	14	(56%)
Pancreatic, congestion	1	(5%)						
Pancreatic, hyperplasia, lymphoid	2	(9%)	2	(8%)	2	(8%)	2	(8%)
Lymph node, mesenteric	(50)		(50)		(49)		(50)	
Congestion					1	(2%)	1	(2%)
Hyperplasia, lymphoid			5	(10%)	2	(4%)	2	(4%)
Spleen	(50)		(50)		(49)		(49)	
Fibrosis	2	(4%)	2	(4%)	2	(4%)		
Hematopoietic cell proliferation	2	(4%)	4	(8%)	7	(14%)	5	(10%)
Hemorrhage							1	(2%)
Necrosis			2	(4%)	2	(4%)	2	(4%)
Pigmentation	4	(8%)	1	(2%)	4	(8%)		
Lymphoid follicle, hyperplasia	1	(2%)						
Thymus	(49)		(48)		(48)		(50)	
Cyst							2	(4%)
Hemorrhage	1	(2%)	2	(4%)	3	(6%)	2	(4%)
Integumentary System								
Mammary gland	(50)		(50)		(50)		(50)	
Cyst	15	(30%)	17	(34%)	17	(34%)	8	(16%)
Skin	(50)		(50)		(50)		(50)	
Cyst epithelial inclusion	4	(8%)	2	(4%)	4	(8%)	1	(2%)
Hyperkeratosis	1	(2%)						
Hyperplasia			1	(2%)				
Inflammation, chronic					2	(4%)	1	(2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hypertrophy		1 (2%)		
Cranium, osteopetrosis				1 (2%)
Skeletal muscle	(2)	(1)	(1)	(3)
Hemorrhage				1 (33%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	7 (14%)	5 (10%)	7 (14%)	2 (4%)
Hemorrhage	1 (2%)	3 (6%)	3 (6%)	3 (6%)
Necrosis		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	6 (12%)	2 (4%)	6 (12%)	2 (4%)
Hemorrhage	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte	31 (62%)	27 (54%)	26 (52%)	28 (56%)
Inflammation, chronic	29 (58%)	28 (56%)	27 (54%)	35 (70%)
Inflammation, suppurative				1 (2%)
Alveolar epithelium, hyperplasia	6 (12%)	5 (10%)	10 (20%)	11 (22%)
Nose	(49)	(50)	(49)	(50)
Foreign body	10 (20%)	8 (16%)	10 (20%)	8 (16%)
Inflammation, chronic	14 (29%)	13 (26%)	14 (29%)	14 (28%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Cataract	3 (6%)			
Inflammation, chronic	2 (4%)			1 (2%)
Harderian gland	(50)	(50)	(49)	(50)
Inflammation, chronic	1 (2%)			1 (2%)
Lacrimal gland				(1)
Inflammation, suppurative				1 (100%)
Urinary System				
Kidney	(49)	(50)	(49)	(50)
Cyst	2 (4%)			1 (2%)
Hydronephrosis	1 (2%)		1 (2%)	
Infarct	1 (2%)	1 (2%)		1 (2%)
Nephropathy	43 (88%)	48 (96%)	46 (94%)	47 (94%)
Capsule, hemorrhage			1 (2%)	
Transitional epithelium, hyperplasia	3 (6%)	9 (18%)	8 (16%)	3 (6%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		2 (4%)		
Inflammation, chronic			1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF DIBROMOACETIC ACID

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Disposition Summary								
Animals initially in study	50		50		50		50	
Early deaths								
Moribund	4		5		9		14	
Natural deaths	11		6		6		4	
Survivors								
Died last week of study			1		1			
Terminal sacrifice	35		38		34		32	
Animals examined microscopically	50		50		50		50	
Alimentary System								
Intestine large, rectum	(49)		(50)		(50)		(48)	
Polyp adenomatous							1	(2%)
Liver	(50)		(50)		(50)		(50)	
Hepatocellular carcinoma					1	(2%)	1	(2%)
Hepatocellular adenoma	2	(4%)					1	(2%)
Histiocytic sarcoma							1	(2%)
Serosa, osteosarcoma, metastatic, bone							1	(2%)
Mesentery	(12)		(15)		(15)		(8)	
Osteosarcoma, metastatic, bone							1	(13%)
Oral mucosa			(1)		(1)		(1)	
Pharyngeal, squamous cell papilloma			1	(100%)			1	(100%)
Pancreas	(47)		(50)		(49)		(48)	
Acinus, adenoma							1	(2%)
Salivary glands	(50)		(50)		(50)		(50)	
Carcinoma, metastatic, mammary gland					1	(2%)		
Stomach, forestomach	(50)		(50)		(50)		(50)	
Squamous cell papilloma	1	(2%)						
Stomach, glandular	(49)		(50)		(50)		(49)	
Tongue							(1)	
Squamous cell papilloma							1	(100%)
Cardiovascular System								
Heart	(50)		(50)		(50)		(50)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1	(2%)				
Endocrine System								
Adrenal cortex	(49)		(50)		(50)		(49)	
Adenoma	1	(2%)						
Adrenal medulla	(49)		(50)		(50)		(49)	
Pheochromocytoma benign	1	(2%)	3	(6%)	2	(4%)	1	(2%)
Parathyroid gland	(50)		(48)		(49)		(47)	
Adenoma							1	(2%)
Pituitary gland	(50)		(50)		(50)		(49)	
Histiocytic sarcoma							1	(2%)
Pars distalis, adenoma	25	(50%)	27	(54%)	27	(54%)	22	(45%)
Pars distalis, adenoma, multiple	1	(2%)	3	(6%)	1	(2%)		
Pars distalis, carcinoma			1	(2%)			1	(2%)
Pars intermedia, adenoma	1	(2%)						

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Endocrine System (continued)								
Thyroid gland	(50)		(50)		(50)		(49)	
Bilateral, C-cell, adenoma	1	(2%)	1	(2%)				
C-cell, adenoma	5	(10%)	10	(20%)	5	(10%)	5	(10%)
C-cell, carcinoma			1	(2%)				
Follicular cell, adenoma							2	(4%)
Follicular cell, carcinoma			1	(2%)	1	(2%)		
General Body System								
None								
Genital System								
Clitoral gland	(50)		(50)		(48)		(49)	
Adenoma	7	(14%)	10	(20%)	5	(10%)	3	(6%)
Carcinoma	1	(2%)	6	(12%)	1	(2%)	5	(10%)
Squamous cell papilloma							1	(2%)
Bilateral, adenoma	1	(2%)						
Ovary	(50)		(50)		(50)		(50)	
Uterus	(50)		(50)		(50)		(50)	
Adenoma							1	(2%)
Deciduoma NOS			1	(2%)			1	(2%)
Polyp stromal	3	(6%)	10	(20%)	7	(14%)	4	(8%)
Bilateral, polyp stromal							1	(2%)
Cervix, polyp stromal	1	(2%)						
Cervix, sarcoma stromal					1	(2%)		
Vagina	(1)		(4)		(6)		(20)	
Polyp adenomatous					1	(17%)		
Sarcoma stromal					1	(17%)		
Hematopoietic System								
Bone marrow	(50)		(50)		(50)		(50)	
Histiocytic sarcoma					1	(2%)	1	(2%)
Lymph node	(13)		(13)		(9)		(21)	
Mediastinal, carcinoma, metastatic, thyroid gland			1	(8%)				
Mediastinal, osteosarcoma, metastatic, bone							1	(5%)
Pancreatic, histiocytic sarcoma							1	(5%)
Lymph node, mandibular	(2)				(1)		(3)	
Lymph node, mesenteric	(49)		(50)		(50)		(48)	
Spleen	(47)		(49)		(50)		(48)	
Histiocytic sarcoma							1	(2%)
Capsule, osteosarcoma, metastatic, bone							1	(2%)
Thymus	(49)		(49)		(50)		(50)	
Integumentary System								
Mammary gland	(50)		(50)		(50)		(50)	
Adenoma			1	(2%)				
Carcinoma	2	(4%)	1	(2%)	1	(2%)	1	(2%)
Carcinoma, multiple	1	(2%)			1	(2%)		
Fibroadenoma	22	(44%)	18	(36%)	11	(22%)	13	(26%)
Fibroadenoma, multiple	10	(20%)	15	(30%)	28	(56%)	23	(46%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Integumentary System (continued)								
Skin	(50)		(50)		(50)		(50)	
Squamous cell papilloma	1	(2%)	1	(2%)			1	(2%)
Squamous cell papilloma, multiple					1	(2%)		
Trichoepithelioma							1	(2%)
Pinna, neural crest tumor							1	(2%)
Subcutaneous tissue, fibroma	1	(2%)						
Musculoskeletal System								
Bone	(50)		(50)		(50)		(50)	
Osteoma					1	(2%)		
Osteosarcoma							1	(2%)
Cranium, meningioma malignant, metastatic, brain	1	(2%)						
Skeletal muscle			(1)				(1)	
Osteosarcoma, metastatic, bone							1	(100%)
Rhabdomyosarcoma			1	(100%)				
Nervous System								
Brain	(50)		(50)		(50)		(50)	
Astrocytoma malignant							1	(2%)
Carcinoma, metastatic, pituitary gland			1	(2%)				
Glioma malignant, mixed cell					1	(2%)		
Meningioma malignant	1	(2%)						
Spinal cord	(2)		(4)		(1)		(1)	
Respiratory System								
Lung	(50)		(50)		(50)		(50)	
Alveolar/bronchiolar adenoma	1	(2%)	1	(2%)	2	(4%)	3	(6%)
Alveolar/bronchiolar carcinoma			1	(2%)			1	(2%)
Alveolar/bronchiolar carcinoma, multiple	1	(2%)	1	(2%)			1	(2%)
Carcinoma, metastatic, thyroid gland			1	(2%)				
Hepatocellular carcinoma, metastatic, liver							1	(2%)
Histiocytic sarcoma							1	(2%)
Osteosarcoma, metastatic, bone							1	(2%)
Nose	(50)		(50)		(50)		(50)	
Pleura			(1)					
Alveolar/bronchiolar carcinoma, metastatic, lung			1	(100%)				
Special Senses System								
Harderian gland	(50)		(50)		(50)		(50)	
Zymbal's gland	(1)						(2)	
Carcinoma	1	(100%)					2	(100%)
Urinary System								
Kidney		(50)		(50)		(50)		(50)
Renal tubule, adenoma			1	(2%)				
Transitional epithelium, carcinoma					1	(2%)		
Urinary bladder		(50)		(50)		(50)		(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia mononuclear	11 (22%)	13 (26%)	16 (32%)	22 (44%)
Mesothelioma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	49	48	49
Total primary neoplasms	103	129	118	126
Total animals with benign neoplasms	42	47	43	43
Total benign neoplasms	85	102	91	87
Total animals with malignant neoplasms	16	24	20	32
Total malignant neoplasms	18	26	27	37
Total animals with metastatic neoplasms	1	3	1	2
Total metastatic neoplasms	1	5	1	7
Total animals with uncertain neoplasms-benign or malignant		1		2
Total uncertain neoplasms		1		2

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	16 19	51 95	59 05	60 02	60 04	60 05	61 51	63 12	63 23	64 30	64 41	65 11	66 05	70 01	70 12	73 34	73 44	73 44	73 44	73 34	73 44	73 44	73 44	73 44	73 45	73 35
Carcass ID Number	20 02	22 27	25 20	22 04	22 49	21 55	23 56	20 44	24 01	20 11	21 18	23 30	24 06	20 66	23 35	21 11	21 12	21 13	21 14	24 42	24 23	24 44	24 45	24 16	21 67	21 17
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X	X								
Mesentery		+		+		+	+	+												+		+				
Pancreas	+	+	+	+	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+		+	+	+		+				+			+					+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X						X		X	X				X	X	X		X		X	X	X
Pars distalis, adenoma, multiple																X										
Pars intermedia, adenoma								X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma			X																							
C-cell, adenoma																			X							X
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X								X	X						
Carcinoma																										
Bilateral, adenoma																										

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	
Carcass ID Number	21 9	22 0	22 1	22 2	22 3	22 5	24 7	24 8	24 9	20 3	20 5	22 6	22 8	23 1	23 2	23 3	23 4	20 7	20 8	20 9	21 0	23 7	23 8	23 9	24 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										2
Mesentery		+	+	+																			+	+		12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma			X																							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel													+						+							10
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X			X	X			X	X					X	X	X	X			X	25
Pars distalis, adenoma, multiple																										1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma	X				X											X										5
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X										X	X			X			7
Carcinoma													X													1
Bilateral, adenoma																X										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	16 11	51 99	59 55	60 02	60 04	60 05	61 11	63 12	63 23	64 30	64 41	65 11	66 15	66 45	70 11	70 12	73 34	73 44	73 44	73 44	73 44	73 44	73 44	73 44	73 45	73 45
Carcass ID Number	20 02	22 27	25 20	22 04	22 49	21 55	23 66	20 44	24 01	20 11	21 18	23 30	24 06	20 66	23 65	21 11	21 12	21 23	21 14	24 42	24 43	24 44	24 45	24 44	21 16	21 17
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X										X												
Cervix, polyp stromal																										
Vagina									+																	
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+			+			+					+					+								
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Carcinoma, multiple																										
Fibroadenoma				X			X			X			X			X		X		X	X	X			X
Fibroadenoma, multiple														X			X		X					X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Subcutaneous tissue, fibroma																								X		
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, meningioma malignant, metastatic, brain								X																		
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma malignant								X																		
Peripheral nerve								+																		
Spinal cord								+																		
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma, multiple								X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3	2 2 5	2 4 7	2 4 8	2 4 9	2 0 3	2 0 5	2 2 6	2 2 8	2 3 1	2 3 2	2 3 3	2 3 4	2 0 7	2 0 8	2 0 9	2 1 0	2 3 7	2 3 8	2 3 9	2 4 0	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																								X		3
Cervix, polyp stromal																						X				1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+							+					+								+		+	13
Lymph node, mandibular	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	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X															X	2
Carcinoma, multiple													X													1
Fibroadenoma	X							X	X	X		X	X			X		X	X	X	X				X	22
Fibroadenoma, multiple			X	X		X	X															X	X			10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, meningioma malignant, metastatic, brain																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma malignant																										1
Peripheral nerve																		+								2
Spinal cord																		+								2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													1
Alveolar/bronchiolar carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	1 6 1	5 1 9	5 9 5	6 0 2	6 0 4	6 0 5	6 1 1	6 3 2	6 3 3	6 4 0	6 4 1	6 5 1	6 6 5	7 0 1	7 0 2	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5
Carcass ID Number	2 0 2	2 2 7	2 5 0	2 2 4	2 2 9	2 1 5	2 3 6	2 0 4	2 4 1	2 0 1	2 1 8	2 3 0	2 4 6	2 0 6	2 3 5	2 1 1	2 1 2	2 1 3	2 1 4	2 4 2	2 4 3	2 4 4	2 4 5	2 1 6	2 1 7
Special Senses System																								
Ear											+			+										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland		+																						
Carcinoma		X																						
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X		X						X			X				X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3	2 2 5	2 4 7	2 4 8	2 4 9	2 0 3	2 0 5	2 2 6	2 2 8	2 3 1	2 3 2	2 3 3	2 3 4	2 0 7	2 0 8	2 0 9	2 1 0	2 3 7	2 3 8	2 3 9	2 4 0	Total Tissues/ Tumors
Special Senses System																										
Ear																										2
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X				X											X						X		11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	3 9 2	5 0 9	5 2 0	5 2 1	6 6 9	6 8 2	6 8 2	6 9 9	7 0 0	7 0 1	7 2 0	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 7 0	2 6 8	2 8 5	2 8 3	2 8 2	2 6 9	2 7 2	2 5 4	2 7 9	2 6 4	2 9 3	2 8 9	2 6 6	2 6 7	2 7 1	2 7 3	2 7 4	2 7 5	2 6 1	2 6 2	2 6 3	2 6 5	2 6 6	2 8 7	2 8 8
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+	+						+			+				+								
Oral mucosa													+											
Pharyngeal, squamous cell papilloma													X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel				+													+					+	+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X					X								
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X				X			X		X	X	X		X	X	X	X	X			X		X
Pars distalis, adenoma, multiple							X			X														
Pars distalis, carcinoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																				X				
C-cell, adenoma																					X	X	X	X
C-cell, carcinoma																		X						
Follicular cell, carcinoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X	X						X		X							X	
Carcinoma	X								X															X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	735	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29 90	25 01	25 12	25 23	25 35	25 56	25 57	25 58	25 59	26 60	27 76	27 77	27 78	28 80	28 81	28 84	29 91	29 92	29 94	29 95	29 96	29 97	29 98	29 99	30 00	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+				+		+			+	+	+		+					+					+	15
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel		+				+											+					+				8
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung								X																		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X		X	X		X	X	X			X		X		X		X		X			27
Pars distalis, adenoma, multiple									X																	3
Pars distalis, carcinoma														X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma			X				X	X											X					X	X	10
C-cell, carcinoma																										1
Follicular cell, carcinoma									X																	1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X						X	X	X		X				10
Carcinoma															X		X		X							6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	3 9 2	5 0 9	5 2 0	5 2 1	6 6 9	6 8 2	6 8 2	6 9 9	7 0 0	7 0 1	7 2 0	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 7 0	2 6 8	2 8 5	2 8 3	2 8 2	2 6 9	2 7 2	2 5 4	2 7 9	2 6 4	2 9 3	2 8 9	2 6 6	2 6 7	2 7 1	2 7 3	2 7 4	2 7 5	2 6 1	2 6 2	2 6 3	2 6 5	2 8 6	2 8 7	2 8 8
Genital System (continued)																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma NOS																								
Polyp stromal				X	X											X								
Vagina		+	+	+																		+		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+		+				+	+	+									+	+	
Mediastinal, carcinoma, metastatic, thyroid gland																								
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																								
Fibroadenoma				X			X			X	X		X		X			X	X			X		X	X
Fibroadenoma, multiple								X				X					X			X			X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																		
Rhabdomyosarcoma						X																		
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																								
Peripheral nerve							+		+															
Spinal cord							+		+															
Respiratory System																								
Larynx											+													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																X								
Alveolar/bronchiolar carcinoma, multiple																								
Carcinoma, metastatic, thyroid gland																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	735	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29 90	25 01	25 02	25 03	25 05	25 06	25 07	25 08	25 09	26 00	27 06	27 07	27 08	28 00	28 01	28 04	29 01	29 02	29 04	29 05	29 06	29 07	29 08	29 09	30 00	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma NOS								X																		1
Polyp stromal	X			X			X				X					X	X				X					10
Vagina																										4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+				+						+	+	+									13
Mediastinal, carcinoma, metastatic, thyroid gland									X																	1
Lymph node, mandibular	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	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Carcinoma										X																1
Fibroadenoma	X						X				X			X				X		X			X			18
Fibroadenoma, multiple		X	X		X			X				X			X	X	X				X	X				15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland														X												1
Peripheral nerve					+					+																4
Spinal cord					+					+																4
Respiratory System																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													1
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple								X																		1
Carcinoma, metastatic, thyroid gland									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	3 9 2	5 0 9	5 2 0	5 2 1	6 6 9	6 8 2	6 8 2	6 9 9	7 0 0	7 0 1	7 2 0	7 2 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 7 0	2 6 8	2 8 5	2 8 3	2 8 2	2 6 9	2 7 2	2 5 4	2 7 9	2 6 4	2 9 3	2 8 9	2 6 6	2 6 7	2 7 1	2 7 3	2 7 4	2 7 5	2 6 1	2 6 2	2 6 3	2 6 5	2 8 6	2 8 7	2 8 8
Respiratory System (continued)																								
Pleura																								
Alveolar/bronchiolar carcinoma, metastatic, lung																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear				+																		+		
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland											+													
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma															X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X	X			X	X									X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 9 0	2 5 1	2 5 2	2 5 3	2 5 5	2 5 6	2 5 7	2 5 8	2 5 9	2 6 0	2 6 6	2 7 7	2 7 8	2 8 0	2 8 1	2 8 4	2 9 1	2 9 2	2 9 4	2 9 5	2 9 6	2 9 7	2 9 8	2 9 9	3 0 0	Total Tissues/ Tumors
Respiratory System (continued)																										
Pleura								+																		1
Alveolar/bronchiolar carcinoma, metastatic, lung								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear						+																+				4
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X											X			X	X							X			13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 0 5	3 0 6	3 0 7	3 0 8	3 0 9	3 1 0	3 1 1	3 1 2	3 1 4	3 4 1	3 4 2	3 4 3	3 2 6	3 2 8	3 2 9	3 3 0	3 1 6	3 2 0	3 3 1	3 3 3	3 3 4	3 3 5	3 3 7	3 3 8	3 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X						1
Mesentery	+				+	+	+	+											+		+		+			15
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland																				X						1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel							+													+				+	9
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																							X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X			X	X					X	X	X	X		X		X	X			X	27
Pars distalis, adenoma, multiple																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																	X			X	5
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X			X									X											X	5
Carcinoma																							X			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X	X			X			X																7
Cervix, sarcoma stromal																										1
Vagina				+			+		+																	6
Polyp adenomatous																										1
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	4 3 0	4 4 1	5 0 6	5 1 9	6 1 8	6 2 2	6 2 2	6 2 4	6 4 0	6 5 1	6 5 7	6 9 6	7 0 1	7 1 4	7 1 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 1 1 7	3 4 5	3 5 0	3 1 9	3 1 8	3 1 3	3 2 5	3 2 2	3 3 4	3 4 8	3 1 5	3 2 4	3 3 9	3 3 6	3 2 7	3 2 1	3 2 2	3 2 3	3 4 6	3 4 7	3 4 9	3 0 1	3 0 2	3 0 3	3 0 4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node					+		+		+	+		+													+
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Carcinoma, multiple																									
Fibroadenoma		X												X						X		X			X
Fibroadenoma, multiple						X	X			X		X	X		X			X	X		X		X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant, mixed cell																									
Peripheral nerve																+									
Spinal cord																+									
Respiratory System																									
Larynx	+																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear						+					+														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 0 0 5	3 0 0 6	3 0 0 7	3 0 0 8	3 0 0 9	3 0 1 0	3 1 1 1	3 1 1 2	3 1 1 4	3 1 4 1	3 4 4 2	3 4 4 3	3 2 2 6	3 2 2 8	3 2 2 9	3 3 0 0	3 1 6 6	3 2 0 0	3 2 3 1	3 3 3 3	3 3 3 4	3 3 3 5	3 3 3 7	3 3 4 8	3 4 0	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X															1
Lymph node				+			+								+											9
Lymph node, mandibular	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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Carcinoma, multiple																				X						1
Fibroadenoma			X							X		X								X		X	X			11
Fibroadenoma, multiple	X	X		X	X	X	X	X	X		X		X	X	X	X	X	X	X					X	X	28
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma, multiple																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma																				X						1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant, mixed cell										X																1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																				+					+	4
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																				+						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	4 3 0	4 4 1	5 0 6	5 1 9	6 1 8	6 2 2	6 2 2	6 2 4	6 4 0	6 5 1	6 5 7	6 9 6	7 0 1	7 1 4	7 1 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 1 7	3 4 5	3 5 0	3 1 9	3 1 8	3 1 3	3 2 5	3 3 2	3 4 4	3 4 8	3 1 5	3 2 4	3 3 9	3 3 6	3 2 7	3 2 1	3 2 2	3 2 3	3 4 6	3 4 7	3 4 9	3 0 1	3 0 2	3 0 3	3 0 4
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear				X	X			X			X		X			X						X			X
Mesothelioma malignant													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	30505	30606	30707	30808	30909	31010	31101	31202	31404	31501	34402	34503	34604	32206	32208	32209	33006	31606	32007	32301	33313	33404	33505	33707	33808	34010	Total Tissues/ Tumors
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma											X																1
Leukemia mononuclear	X				X		X				X				X			X		X		X				X	16
Mesothelioma malignant																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	254	359	566	577	580	602	621	622	622	637	651	651	664	664	679	699	682	682	729	729	729	729	729	729	734
Carcass ID Number	38447	37756	35762	38829	37955	35583	38837	40070	37465	36550	37706	37806	38057	35971	37125	35268	35865	35589	36072	37723	37735	37945	39696		
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, cecum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																					X				
Histiocytic sarcoma																									
Serosa, osteosarcoma, metastatic, bone							X																		
Mesentery					+		+							+									+		
Osteosarcoma, metastatic, bone							X																		
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue														+											
Squamous cell papilloma														X											
Cardiovascular System																									
Blood vessel					+		+					+												+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Pituitary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Pars distalis, adenoma						X			X			X	X				X	X	X		X	X	X		
Pars distalis, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X					X	X								X					
Follicular cell, adenoma																				X					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 9 7	3 9 8	3 9 9	3 6 1	3 6 2	3 6 3	3 6 4	3 7 8	3 8 1	3 8 5	3 8 8	3 8 9	3 9 0	3 5 1	3 5 3	3 5 4	3 6 6	3 6 7	3 6 8	3 6 9	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous		X																								1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma														X												1
Hepatocellular adenoma																										1
Histiocytic sarcoma					X																					1
Serosa, osteosarcoma, metastatic, bone																										1
Mesentery	+		+										+					+								8
Osteosarcoma, metastatic, bone																										1
Oral mucosa										+																1
Pharyngeal, squamous cell papilloma										X																1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel					+	+				+					+						+	+			+	11
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	47
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma					X																					1
Pars distalis, adenoma	X	X				X			X			X		X		X	X	X			X	X		X		22
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																	X									5
Follicular cell, adenoma																								X		2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	254	359	556	577	580	602	621	622	622	637	651	651	664	664	679	699	822	822	929	929	929	929	929	934
Carcass ID Number	38447	37756	35762	38829	37955	35755	38833	38877	40400	37744	36455	37706	37766	38804	35571	37112	35126	38626	35589	35590	36002	37723	37735	39696
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma					X									X		X					X			
Squamous cell papilloma			X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Deciduoma NOS									X															
Polyp stromal															X									
Bilateral, polyp stromal																							X	
Vagina				+					+		+		+	+			+						+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymph node		+		+		+	+	+			+		+	+	+	+	+	+			+	+		
Mediastinal, osteosarcoma, metastatic, bone							X																	
Pancreatic, histiocytic sarcoma																								
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Capsule, osteosarcoma, metastatic, bone							X																	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Fibroadenoma				X		X								X							X			X
Fibroadenoma, multiple									X							X	X		X	X		X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X						
Trichoepithelioma																								
Pinna, neural crest tumor															X									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma							X																	
Skeletal muscle							+																	
Osteosarcoma, metastatic, bone							X																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 9 7	3 9 8	3 9 9	3 6 1	3 6 2	3 6 3	3 6 4	3 7 8	3 8 1	3 8 5	3 8 8	3 8 9	3 9 0	3 5 1	3 5 3	3 5 4	3 6 6	3 6 7	3 6 8	3 6 9	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X								X					X					3
Carcinoma							X																			5
Squamous cell papilloma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Deciduoma NOS																										1
Polyp stromal							X												X			X				4
Bilateral, polyp stromal																										1
Vagina					+	+	+			+	+	+		+	+	+		+					+	+		20
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																					1
Lymph node		+		M	+				+		+	+			+							+				21
Mediastinal, osteosarcoma, metastatic, bone																										1
Pancreatic, histiocytic sarcoma					X																					1
Lymph node, mandibular	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma					X																					1
Capsule, osteosarcoma, metastatic, bone																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		1
Fibroadenoma							X			X		X	X			X		X			X		X			13
Fibroadenoma, multiple	X	X	X	X	X	X		X	X		X			X			X		X	X		X		X	X	23
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Trichoepithelioma										X																1
Pinna, neural crest tumor																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Osteosarcoma, metastatic, bone																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	254	395	566	577	580	602	621	622	622	637	651	651	664	664	679	679	682	682	722	729	729	729	729	729	734
Carcass ID Number	38447	37596	35662	38729	37955	35953	38837	38707	40404	37374	36545	37010	37766	38060	35771	37112	35126	35826	35589	36072	37723	37735	37796	39606
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X	X	
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear												+													
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland												+	+												
Carcinoma												X	X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear		X		X		X		X			X			X	X	X	X	X			X	X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 9 7	3 9 8	3 9 9	3 6 1	3 6 2	3 6 3	3 6 4	3 7 8	3 8 1	3 8 5	3 8 8	3 8 9	3 9 0	3 5 1	3 5 3	3 5 4	3 6 6	3 6 7	3 6 8	3 6 9	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant											X															1
Peripheral nerve																+										1
Spinal cord																+										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				3
Alveolar/bronchiolar carcinoma																					X					1
Alveolar/bronchiolar carcinoma, multiple															X											1
Hepatocellular carcinoma, metastatic, liver														X												1
Histiocytic sarcoma					X																					1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear						+																+				3
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																					1
Leukemia mononuclear		X	X			X					X	X				X		X	X			X		X		22

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	1/49 (2%)	3/50 (6%)	2/50 (4%)	1/49 (2%)
Adjusted rate[b]	2.3%	6.5%	4.5%	2.4%
Terminal rate[c]	1/35 (3%)	2/39 (5%)	2/35 (6%)	1/32 (3%)
First incidence (days)	729 (T)	720	729 (T)	729 (T)
Poly-3 test[d]	P=0.396N	P=0.330	P=0.509	P=0.757
Clitoral Gland: Adenoma				
Overall rate	8/50 (16%)	10/50 (20%)	5/48 (10%)	3/49 (6%)
Adjusted rate	18.0%	21.5%	11.8%	7.2%
Terminal rate	7/35 (20%)	8/39 (21%)	5/33 (15%)	3/31 (10%)
First incidence (days)	641	682	729 (T)	729 (T)
Poly-3 test	P=0.033N	P=0.439	P=0.306N	P=0.116N
Clitoral Gland: Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	1/48 (2%)	5/49 (10%)
Adjusted rate	2.3%	12.7%	2.4%	11.7%
Terminal rate	1/35 (3%)	4/39 (10%)	1/33 (3%)	2/31 (7%)
First incidence (days)	729 (T)	392	729 (T)	580
Poly-3 test	P=0.335	P=0.068	P=0.752	P=0.094
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	9/50 (18%)	15/50 (30%)	6/48 (13%)	8/49 (16%)
Adjusted rate	20.3%	31.6%	14.2%	18.7%
Terminal rate	8/35 (23%)	11/39 (28%)	6/33 (18%)	5/31 (16%)
First incidence (days)	641	392	729 (T)	580
Poly-3 test	P=0.143N	P=0.158	P=0.321N	P=0.533N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.3%	2.2%	4.5%	7.0%
Terminal rate	1/35 (3%)	1/39 (3%)	2/35 (6%)	3/32 (9%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.137	P=0.750N	P=0.502	P=0.295
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	4.5%	6.5%	4.5%	11.6%
Terminal rate	1/35 (3%)	3/39 (8%)	2/35 (6%)	5/32 (16%)
First incidence (days)	632	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.161	P=0.518	P=0.693	P=0.201
Mammary Gland: Fibroadenoma				
Overall rate	32/50 (64%)	33/50 (66%)	39/50 (78%)	36/50 (72%)
Adjusted rate	70.1%	69.7%	83.8%	80.2%
Terminal rate	27/35 (77%)	28/39 (72%)	31/35 (89%)	30/32 (94%)
First incidence (days)	602	521	441	577
Poly-3 test	P=0.061	P=0.576N	P=0.079	P=0.175
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	2.2%	4.5%	2.3%
Terminal rate	3/35 (9%)	1/39 (3%)	1/35 (3%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	640	729 (T)
Poly-3 test	P=0.371N	P=0.289N	P=0.494N	P=0.315N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	4.3%	4.5%	2.3%
Terminal rate	3/35 (9%)	2/39 (5%)	1/35 (3%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	640	729 (T)
Poly-3 test	P=0.271N	P=0.479N	P=0.494N	P=0.315N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	32/50 (64%)	34/50 (68%)	40/50 (80%)	36/50 (72%)
Adjusted rate	70.1%	71.8%	85.3%	80.2%
Terminal rate	27/35 (77%)	29/39 (74%)	31/35 (89%)	30/32 (94%)
First incidence (days)	602	521	441	577
Poly-3 test	P=0.073	P=0.519	P=0.052	P=0.175
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/50 (52%)	30/50 (60%)	28/50 (56%)	22/49 (45%)
Adjusted rate	55.9%	63.1%	61.3%	49.8%
Terminal rate	20/35 (57%)	24/39 (62%)	22/35 (63%)	16/32 (50%)
First incidence (days)	519	509	622	602
Poly-3 test	P=0.197N	P=0.306	P=0.376	P=0.352N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	26/50 (52%)	31/50 (62%)	28/50 (56%)	23/49 (47%)
Adjusted rate	55.9%	65.2%	61.3%	51.7%
Terminal rate	20/35 (57%)	25/39 (64%)	22/35 (63%)	16/32 (50%)
First incidence (days)	519	509	622	602
Poly-3 test	P=0.214N	P=0.235	P=0.376	P=0.421N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	11/50 (22%)	5/50 (10%)	5/49 (10%)
Adjusted rate	13.5%	23.8%	11.3%	11.6%
Terminal rate	5/35 (14%)	11/39 (28%)	5/35 (14%)	2/32 (6%)
First incidence (days)	595	729 (T)	729 (T)	602
Poly-3 test	P=0.149N	P=0.160	P=0.503N	P=0.521N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	12/50 (24%)	5/50 (10%)	5/49 (10%)
Adjusted rate	13.5%	25.9%	11.3%	11.6%
Terminal rate	5/35 (14%)	12/39 (31%)	5/35 (14%)	2/32 (6%)
First incidence (days)	595	729 (T)	729 (T)	602
Poly-3 test	P=0.115N	P=0.108	P=0.503N	P=0.521N
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	10/50 (20%)	7/50 (14%)	5/50 (10%)
Adjusted rate	9.0%	21.2%	15.7%	11.6%
Terminal rate	2/35 (6%)	8/39 (21%)	6/35 (17%)	4/32 (13%)
First incidence (days)	602	521	701	679
Poly-3 test	P=0.374N	P=0.088	P=0.257	P=0.478
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/50 (8%)	10/50 (20%)	8/50 (16%)	5/50 (10%)
Adjusted rate	9.0%	21.2%	17.7%	11.6%
Terminal rate	2/35 (6%)	8/39 (21%)	6/35 (17%)	4/32 (13%)
First incidence (days)	602	521	519	679
Poly-3 test	P=0.400N	P=0.088	P=0.180	P=0.478

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
All Organs: Mononuclear Cell Leukemia				
Overall rate	11/50 (22%)	13/50 (26%)	16/50 (32%)	22/50 (44%)
Adjusted rate	24.3%	27.1%	34.7%	47.4%
Terminal rate	8/35 (23%)	8/39 (21%)	11/35 (31%)	12/32 (38%)
First incidence (days)	605	509	519	395
Poly-3 test	P=0.006	P=0.474	P=0.195	P=0.016
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	47/50 (94%)	43/50 (86%)	43/50 (86%)
Adjusted rate	88.1%	96.9%	92.4%	92.6%
Terminal rate	32/35 (91%)	38/39 (97%)	35/35 (100%)	32/32 (100%)
First incidence (days)	519	509	441	566
Poly-3 test	P=0.538	P=0.085	P=0.342	P=0.327
All Organs: Malignant Neoplasms				
Overall rate	16/50 (32%)	24/50 (48%)	20/50 (40%)	32/50 (64%)
Adjusted rate	34.6%	48.9%	43.0%	66.5%
Terminal rate	11/35 (31%)	17/39 (44%)	14/35 (40%)	17/32 (53%)
First incidence (days)	519	392	519	395
Poly-3 test	P=0.004	P=0.112	P=0.267	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	49/50 (98%)	48/50 (96%)	49/50 (98%)
Adjusted rate	92.8%	98.0%	98.9%	99.9%
Terminal rate	33/35 (94%)	38/39 (97%)	35/35 (100%)	32/32 (100%)
First incidence (days)	519	392	441	395
Poly-3 test	P=0.053	P=0.219	P=0.138	P=0.077

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.

TABLE B4
Historical Incidence of Mononuclear Cell Leukemia in Control Female F344/N Rats[a]

	Incidence in Controls
Historical Incidence: Drinking Water Studies	
Dibromoacetic acid	11/50
Dipropylene glycol	10/50
Sodium chlorate	11/50
Sodium nitrite	15/50
Overall Historical Incidence: Drinking Water Studies	
Total (%)	47/200 (23.5%)
Mean ± standard deviation	23.5% ± 4.4%
Range	20%-30%
Overall Historical Incidence	
Total (%)	383/1,459 (26.3%)
Mean ± standard deviation	26.7% ± 10.5%
Range	12%-52%

[a] Data as of January 26, 2005

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Disposition Summary								
Animals initially in study	50		50		50		50	
Early deaths								
Moribund	4		5		9		14	
Natural deaths	11		6		6		4	
Survivors								
Died last week of study			1		1			
Terminal sacrifice	35		38		34		32	
Animals examined microscopically	50		50		50		50	
Alimentary System								
Intestine large, colon	(49)		(49)		(49)		(48)	
Edema							2	(4%)
Inflammation							1	(2%)
Intestine large, rectum	(49)		(50)		(50)		(48)	
Inflammation			1	(2%)				
Intestine small, ileum	(44)		(47)		(45)		(48)	
Inflammation, suppurative					1	(2%)		
Liver	(50)		(50)		(50)		(50)	
Basophilic focus	36	(72%)	41	(82%)	29	(58%)	15	(30%)
Clear cell focus	8	(16%)	4	(8%)	14	(28%)	18	(36%)
Degeneration, cystic							1	(2%)
Eosinophilic focus	4	(8%)	4	(8%)	5	(10%)	9	(18%)
Hematopoietic cell proliferation	1	(2%)						
Hepatodiaphragmatic nodule	3	(6%)	9	(18%)	2	(4%)	5	(10%)
Inflammation, chronic	2	(4%)	3	(6%)	3	(6%)	1	(2%)
Inflammation, granulomatous	8	(16%)			1	(2%)	2	(4%)
Mixed cell focus	1	(2%)	1	(2%)	1	(2%)	4	(8%)
Necrosis, focal	1	(2%)					1	(2%)
Bile duct, hyperplasia	17	(34%)	15	(30%)	15	(30%)	19	(38%)
Centrilobular, necrosis	1	(2%)	1	(2%)			1	(2%)
Hepatocyte, vacuolization cytoplasmic	3	(6%)	2	(4%)			1	(2%)
Hepatocyte, centrilobular, vacuolization cytoplasmic	1	(2%)						
Serosa, fibrosis	2	(4%)	2	(4%)				
Mesentery	(12)		(15)		(15)		(8)	
Accessory spleen	1	(8%)			1	(7%)		
Fat, necrosis	9	(75%)	12	(80%)	14	(93%)	6	(75%)
Pancreas	(47)		(50)		(49)		(48)	
Atrophy	19	(40%)	15	(30%)	20	(41%)	23	(48%)
Cyst	1	(2%)			1	(2%)	1	(2%)
Acinus, hyperplasia, focal	1	(2%)	2	(4%)			2	(4%)
Salivary glands	(50)		(50)		(50)		(50)	
Inflammation					1	(2%)	2	(4%)
Stomach, forestomach	(50)		(50)		(50)		(50)	
Edema	2	(4%)	5	(10%)			1	(2%)
Erosion	1	(2%)	1	(2%)			1	(2%)
Ulcer	3	(6%)	5	(10%)			1	(2%)
Epithelium, hyperplasia			6	(12%)			2	(4%)
Stomach, glandular	(49)		(50)		(50)		(49)	
Edema	1	(2%)	2	(4%)			2	(4%)
Erosion			1	(2%)			2	(4%)
Ulcer			1	(2%)			2	(4%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Cardiovascular System								
Heart	(50)		(50)		(50)		(50)	
Cardiomyopathy	37	(74%)	29	(58%)	34	(68%)	35	(70%)
Mineralization	1	(2%)						
Thrombosis	2	(4%)	1	(2%)	1	(2%)	1	(2%)
Valve, inflammation, suppurative							1	(2%)
Endocrine System								
Adrenal cortex	(49)		(50)		(50)		(49)	
Accessory adrenal cortical nodule	17	(35%)	8	(16%)	6	(12%)	6	(12%)
Degeneration, fatty	14	(29%)	19	(38%)	15	(30%)	14	(29%)
Hyperplasia, focal	8	(16%)	6	(12%)	4	(8%)	5	(10%)
Hypertrophy, focal	18	(37%)	19	(38%)	21	(42%)	17	(35%)
Necrosis	3	(6%)	1	(2%)	1	(2%)	1	(2%)
Adrenal medulla	(49)		(50)		(50)		(49)	
Hyperplasia	5	(10%)	1	(2%)	2	(4%)	4	(8%)
Islets, pancreatic	(47)		(49)		(49)		(48)	
Metaplasia, hepatocyte			1	(2%)			3	(6%)
Pituitary gland	(50)		(50)		(50)		(49)	
Pars distalis, angiectasis	32	(64%)	24	(48%)	23	(46%)	23	(47%)
Pars distalis, cyst	20	(40%)	24	(48%)	20	(40%)	18	(37%)
Pars distalis, hyperplasia, focal	11	(22%)	9	(18%)	8	(16%)	6	(12%)
Pars intermedia, angiectasis					1	(2%)		
Pars intermedia, cyst							1	(2%)
Thyroid gland	(50)		(50)		(50)		(49)	
Ultimobranchial cyst	1	(2%)						
C-cell, hyperplasia	23	(46%)	6	(12%)	18	(36%)	18	(37%)
General Body System								
None								
Genital System								
Clitoral gland	(50)		(50)		(48)		(49)	
Cyst	12	(24%)	4	(8%)	8	(17%)	13	(27%)
Hyperplasia	1	(2%)	4	(8%)			2	(4%)
Inflammation, chronic	3	(6%)	2	(4%)	5	(10%)	3	(6%)
Ovary	(50)		(50)		(50)		(50)	
Cyst	8	(16%)	9	(18%)	14	(28%)	8	(16%)
Uterus	(50)		(50)		(50)		(50)	
Cyst	3	(6%)			1	(2%)	3	(6%)
Hemorrhage	1	(2%)						
Hydrometra	1	(2%)	2	(4%)	1	(2%)		
Inflammation, chronic					1	(2%)	2	(4%)
Cervix, cyst							1	(2%)
Cervix, inflammation, suppurative							1	(2%)
Endometrium, hyperplasia, cystic	2	(4%)	1	(2%)				
Vagina	(1)		(4)		(6)		(20)	
Cyst					3	(50%)	10	(50%)
Inflammation			1	(25%)	1	(17%)	9	(45%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Hematopoietic System								
Bone marrow	(50)		(50)		(50)		(50)	
Depletion cellular	1	(2%)						
Hyperplasia	5	(10%)	8	(16%)	5	(10%)	3	(6%)
Myelofibrosis			1	(2%)			2	(4%)
Lymph node	(13)		(13)		(9)		(21)	
Deep cervical, hemorrhage	1	(8%)						
Deep cervical, hyperplasia							1	(5%)
Mediastinal, congestion					2	(22%)		
Mediastinal, hyperplasia, lymphoid	7	(54%)	4	(31%)	3	(33%)	5	(24%)
Pancreatic, hyperplasia, lymphoid	2	(15%)	4	(31%)	2	(22%)	3	(14%)
Pancreatic, pigmentation	1	(8%)						
Lymph node, mandibular	(2)				(1)		(3)	
Hyperplasia, lymphoid	1	(50%)			1	(100%)		
Lymph node, mesenteric	(49)		(50)		(50)		(48)	
Hyperplasia, lymphoid	1	(2%)					3	(6%)
Hyperplasia, reticulum cell	1	(2%)						
Spleen	(47)		(49)		(50)		(48)	
Fibrosis			3	(6%)	1	(2%)		
Hematopoietic cell proliferation	5	(11%)	16	(33%)	7	(14%)	5	(10%)
Necrosis			2	(4%)				
Pigmentation	8	(17%)	9	(18%)	6	(12%)	1	(2%)
Lymphoid follicle, hyperplasia	1	(2%)			1	(2%)	1	(2%)
Thymus	(49)		(49)		(50)		(50)	
Hemorrhage	2	(4%)			1	(2%)		
Integumentary System								
Mammary gland	(50)		(50)		(50)		(50)	
Cyst	45	(90%)	48	(96%)	41	(82%)	37	(74%)
Galactocele			1	(2%)	1	(2%)		
Hyperplasia	2	(4%)	3	(6%)	4	(8%)	2	(4%)
Hyperplasia, atypical	5	(10%)	2	(4%)	4	(8%)	4	(8%)
Hyperplasia, lobular							1	(2%)
Skin	(50)		(50)		(50)		(50)	
Cyst epithelial inclusion			2	(4%)			1	(2%)
Hemorrhage							1	(2%)
Inflammation, chronic	1	(2%)	3	(6%)	3	(6%)		
Musculoskeletal System								
None								
Nervous System								
Brain	(50)		(50)		(50)		(50)	
Compression	6	(12%)	9	(18%)	7	(14%)	5	(10%)
Hemorrhage	1	(2%)	5	(10%)	2	(4%)	3	(6%)
Necrosis			2	(4%)			1	(2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Respiratory System								
Larynx			(1)		(1)			
Inflammation, chronic, suppurative					1	(100%)		
Lung	(50)		(50)		(50)		(50)	
Congestion	4	(8%)	2	(4%)	5	(10%)	3	(6%)
Hemorrhage	1	(2%)	1	(2%)			1	(2%)
Infiltration cellular, histiocyte	45	(90%)	47	(94%)	46	(92%)	45	(90%)
Inflammation, chronic	31	(62%)	31	(62%)	40	(80%)	36	(72%)
Alveolar epithelium, hyperplasia	3	(6%)	7	(14%)	13	(26%)	14	(28%)
Nose	(50)		(50)		(50)		(50)	
Foreign body			2	(4%)	1	(2%)	1	(2%)
Inflammation, chronic	2	(4%)	3	(6%)	4	(8%)	6	(12%)
Inflammation, suppurative							1	(2%)
Respiratory epithelium, hyperplasia							1	(2%)
Special Senses System								
Eye	(50)		(50)		(50)		(50)	
Cataract	2	(4%)	2	(4%)	2	(4%)	1	(2%)
Inflammation, chronic	1	(2%)					2	(4%)
Urinary System								
Kidney	(50)		(50)		(50)		(50)	
Hydronephrosis			1	(2%)	1	(2%)		
Infarct			2	(4%)			2	(4%)
Inflammation, chronic							2	(4%)
Nephropathy	18	(36%)	32	(64%)	37	(74%)	40	(80%)
Renal tubule, hyperplasia			1	(2%)				
Transitional epithelium, hyperplasia					2	(4%)	2	(4%)
Urinary bladder	(50)		(50)		(50)		(50)	
Hemorrhage					1	(2%)		
Inflammation, chronic					1	(2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF DIBROMOACETIC ACID

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Other	1			
Moribund	4	6	3	6
Natural deaths	14	6	13	13
Survivors				
Terminal sacrifice	31	38	34	31
Animals examined microscopically	49	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Intestine large, colon	(48)	(50)	(49)	(48)
Carcinoma				1 (2%)
Hemangioma		1 (2%)		
Intestine small, duodenum	(42)	(50)	(46)	(48)
Carcinoma				1 (2%)
Polyp adenomatous		1 (2%)	2 (4%)	1 (2%)
Intestine small, jejunum	(44)	(49)	(46)	(45)
Carcinoma		2 (4%)		3 (7%)
Polyp adenomatous	1 (2%)	1 (2%)		
Intestine small, ileum	(44)	(49)	(47)	(48)
Polyp adenomatous		1 (2%)		
Liver	(49)	(50)	(50)	(50)
Hemangioma			1 (2%)	
Hemangiosarcoma	1 (2%)	2 (4%)		2 (4%)
Hepatoblastoma		4 (8%)	3 (6%)	16 (32%)
Hepatoblastoma, multiple			3 (6%)	2 (4%)
Hepatocellular carcinoma	11 (22%)	7 (14%)	14 (28%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)	2 (4%)	5 (10%)	15 (30%)
Hepatocellular adenoma	12 (24%)	20 (40%)	13 (26%)	15 (30%)
Hepatocellular adenoma, multiple	6 (12%)	17 (34%)	24 (48%)	27 (54%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Sarcoma		1 (2%)		
Mesentery	(7)	(7)	(10)	(7)
Hepatoblastoma, metastatic, liver			1 (10%)	1 (14%)
Osteosarcoma, metastatic, bone			1 (10%)	
Sarcoma		1 (14%)		
Pancreas	(46)	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		1 (2%)
Acinus, carcinoma		1 (2%)		
Acinus, sarcoma		1 (2%)		
Salivary glands	(49)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(50)
Sarcoma		1 (2%)		
Squamous cell carcinoma	1 (2%)	1 (2%)		
Squamous cell papilloma				1 (2%)
Stomach, glandular	(47)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adenoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver				2 (4%)
Capsule, adenoma	3 (6%)	3 (6%)	2 (4%)	
Capsule, carcinoma		1 (2%)		
Adrenal medulla	(49)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(46)	(50)	(50)	(49)
Adenoma		2 (4%)	4 (8%)	3 (6%)
Adenoma, multiple		1 (2%)		
Thyroid gland	(48)	(50)	(50)	(50)
Follicular cell, adenoma			1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland		(1)	(1)	
Hemangioma			1 (100%)	
Prostate	(48)	(50)	(50)	(49)
Carcinoma, metastatic, pancreas		1 (2%)		
Testes	(49)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Interstitial cell, adenoma		2 (4%)		1 (2%)
Hematopoietic System				
Bone marrow	(47)	(50)	(50)	(50)
Lymph node	(1)	(2)	(5)	(1)
Iliac, carcinoma, metastatic, pancreas		1 (50%)		
Renal, carcinoma, metastatic, pancreas		1 (50%)		
Lymph node, mandibular	(48)	(50)	(48)	(48)
Lymph node, mesenteric	(46)	(49)	(49)	(47)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Spleen	(47)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)	3 (6%)		
Hepatoblastoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Thymus	(42)	(45)	(46)	(47)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Basal cell carcinoma			1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)			
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, fibrous histiocytoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Osteosarcoma			1 (2%)	
Skeletal muscle	(1)	(1)		(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)
Sarcoma		1 (100%)		
Nervous System				
None				
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	4 (8%)	15 (30%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	7 (14%)	6 (12%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Carcinoma, metastatic, pancreas		1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)	2 (4%)	6 (12%)
Hepatocellular carcinoma, metastatic, liver	8 (16%)	5 (10%)	7 (14%)	13 (26%)
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Bronchus, adenoma	1 (2%)		1 (2%)	
Mediastinum, hepatoblastoma, metastatic, liver				2 (4%)
Special Senses System				
Harderian gland	(49)	(50)	(50)	(50)
Adenoma	3 (6%)	4 (8%)	5 (10%)	6 (12%)
Adenoma, multiple		1 (2%)		1 (2%)
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Renal tubule, adenoma	1 (2%)	1 (2%)		
Systemic Lesions				
Multiple organs[b]	(49)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant		5 (10%)	3 (6%)	2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Neoplasm Summary				
Total animals with primary neoplasms[c]	37	44	49	50
Total primary neoplasms	61	103	110	130
Total animals with benign neoplasms	25	38	42	46
Total benign neoplasms	35	61	71	68
Total animals with malignant neoplasms	23	28	32	43
Total malignant neoplasms	26	42	39	62
Total animals with metastatic neoplasms	9	7	10	21
Total metastatic neoplasms	10	13	13	28

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	43	44	45	48	51	55	60	62	63	63	65	66	66	70	71	71	71	71	72	72	72	72	73	73
	51	51	48	82	44	96	11	66	11	32	55	29	93	00	10	05	17	29	99	99	99	30	30	
Carcass ID Number	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00
	05	11	04	84	44	83	42	71	41	05	36	44	03	94	07	73	18	25	13	22	29	73	30	01
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	A	+	A	M	+	M	+	A	A	A	+	+	A	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	A	+	+	+	A	A	+	A	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	A	A	+	M	+	A	A	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	A	+	+	+	+	+	+	+
Polyp adenomatous																								
Intestine small, ileum	+	+	+	+	A	+	A	+	+	+	M	A	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma		X						X		X	X						X					X		
Hepatocellular carcinoma, multiple									X				X			X								
Hepatocellular adenoma						X	X										X							
Hepatocellular adenoma, multiple														X				X				X		
Pheochromocytoma malignant, metastatic, adrenal medulla														X										
Mesentery												+												
Pancreas	+	+	+	+	+	+	A	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X													
Stomach, glandular	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								
Tooth								+										+						
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																								
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								X
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X										
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
None																								

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 1 2	0 2 6	0 3 2	0 3 3	0 4 8	0 0 2	0 0 6	0 1 5	0 1 6	0 2 0	0 3 4	0 3 9	0 4 3	0 4 5	0 4 6	0 0 1	0 0 8	0 0 9	0 1 4	0 1 9	0 2 3	0 2 7	0 3 1	0 3 5	0 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Polyp adenomatous												X														1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma											X															1
Hepatocellular carcinoma		X		X							X		X		X											11
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma		X			X		X				X					X			X				X	X	X	12
Hepatocellular adenoma, multiple						X				X										X						6
Pheochromocytoma malignant, metastatic, adrenal medulla									+																	1
Mesentery	+		+		+	+															+					7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tongue	+																									1
Tooth																	+		+			+				5
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma			X																							1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma						X																			X	3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	435	451	458	482	514	596	601	626	631	632	655	662	669	703	710	710	711	715	717	729	729	729	729	730	730
Carcass ID Number	00015	00111	00014	00248	00444	00338	00422	00117	00441	00510	00336	00244	00340	00409	00077	00318	00118	00125	00213	00122	00229	00477	00133	00230	00110
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Thymus	+	+	+	+	+	+	+	+	M	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+		+																						
Spinal cord	+		+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X												X			X						
Alveolar/bronchiolar carcinoma															X								X		
Alveolar/bronchiolar carcinoma, multiple												X													X
Hepatocellular carcinoma, metastatic, liver								X	X				X				X	X							
Pheochromocytoma malignant, metastatic, adrenal medulla														X											
Bronchus, adenoma																									
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 1 2	0 2 6	0 3 2	0 3 3	0 4 8	0 0 2	0 0 6	0 1 5	0 1 6	0 2 0	0 3 4	0 3 9	0 4 3	0 4 5	0 4 6	0 0 1	0 0 8	0 0 9	0 1 4	0 1 9	0 2 3	0 2 7	0 3 1	0 3 5	0 4 0	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+		48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																				X							1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node																			+								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma	X																										2
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M		42
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																											2
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X																			X				X	X		7
Alveolar/bronchiolar carcinoma																			X								3
Alveolar/bronchiolar carcinoma, multiple																											2
Hepatocellular carcinoma, metastatic, liver		X									X				X												8
Pheochromocytoma malignant, metastatic, adrenal medulla																											1
Bronchus, adenoma													X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	4 3 5	4 5 1	4 5 8	4 8 2	5 1 4	5 9 6	6 0 1	6 2 6	6 3 1	6 3 2	6 5 5	6 6 2	6 6 9	7 0 3	7 1 0	7 1 0	7 1 5	7 1 7	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0
Carcass ID Number	0 0 5	0 1 1	0 1 4	0 2 8	0 4 4	0 3 8	0 4 2	0 1 7	0 4 1	0 5 0	0 3 6	0 2 4	0 3 0	0 4 9	0 0 7	0 3 7	0 1 8	0 2 5	0 1 3	0 2 2	0 2 9	0 4 7	0 0 3	0 1 0
Special Senses System																							
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	734	734	734	734	
Carcass ID Number	00112	00226	00323	00333	00448	00502	00606	00715	00816	00920	01034	01149	01243	01345	01446	01501	01618	01709	01814	01924	02033	02237	02331	02435	02540	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X														X	X									3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	29	56	57	58	59	65	65	68	69	69	71	72	72	72	72	72	72	73	73	73	73	73	73	73	73
	97	72	33	32	66	99	99	44	00	11	77	11	99	29	99	99	99	00	00	00	00	00	00	00	00
Carcass ID Number	06	07	06	08	09	08	09	09	05	07	09	09	05	06	07	07	08	05	05	05	06	06	07	07	07
	61	77	00	88	00	99	02	11	77	11	55	66	88	88	00	33	22	11	33	99	33	66	44	55	88
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas										X															
Gallbladder	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp adenomatous																X									
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																				X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Hepatoblastoma											X								X						
Hepatocellular carcinoma						X			X										X						
Hepatocellular carcinoma, multiple											X										X				
Hepatocellular adenoma			X		X				X	X					X			X	X		X	X			
Hepatocellular adenoma, multiple								X				X		X		X	X			X			X		X
Sarcoma					X																				
Mesentery					+			+							+			+							+
Sarcoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																			X						
Acinus, carcinoma										X															
Acinus, sarcoma					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma					X																				
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma							X																		
Capsule, carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	734	734	
Carcass ID Number	08 81	08 85	08 87	09 94	09 98	10 00	05 02	05 55	06 02	06 04	06 05	06 07	06 09	07 02	07 09	08 86	09 99	05 44	05 56	07 66	08 00	08 83	08 44	09 43	09 97	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																			1
Intestine large, rectum	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous								X																		1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma				X		X																				2
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								2
Hepatoblastoma										X						X										4
Hepatocellular carcinoma		X											X					X					X			7
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma				X	X		X	X		X	X	X		X		X		X	X							20
Hepatocellular adenoma, multiple						X							X		X		X			X	X	X		X	X	17
Sarcoma																										1
Mesentery																+	+									7
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Acinus, carcinoma																										1
Acinus, sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Squamous cell carcinoma												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+			+		+		+				+												6
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Capsule, adenoma					X												X									3
Capsule, carcinoma																								X		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	29	56	57	58	59	65	65	68	69	69	71	72	72	72	72	72	72	73	73	73	73	73	73	73	73
	97	22	33	32	66	99	99	44	00	01	77	21	99	99	99	99	99	00	00	00	00	00	00	00	00
Carcass ID Number	06	07	06	08	09	08	09	09	05	07	09	09	55	66	77	83	82	15	53	59	63	66	64	75	78
	11	17	10	18	10	19	12	11	17	11	15	16	18	18	10	13	12	11	13	19	13	16	14	15	18
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Adenoma, multiple																									
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Coagulating gland										+															
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas										X															
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+		+															
Iliac, carcinoma, metastatic, pancreas										X															
Renal, carcinoma, metastatic, pancreas										X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X				X				X			
Hepatoblastoma, metastatic, liver											X														
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Sarcoma					X																				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 8 1	0 8 5	0 8 7	0 9 4	0 9 8	1 0 0	0 5 2	0 5 5	0 6 2	0 6 4	0 6 5	0 6 7	0 6 9	0 7 2	0 7 9	0 8 6	0 9 9	0 5 4	0 5 6	0 7 6	0 8 0	0 8 3	0 8 4	0 9 3	0 9 7	Total Tissues/ Tumors
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			2
Adenoma, multiple													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma												X				X										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Iliac, carcinoma, metastatic, pancreas																										1
Renal, carcinoma, metastatic, pancreas																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Hepatoblastoma, metastatic, liver																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	I	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	29	56	57	58	59	65	65	68	69	69	71	72	72	72	72	72	72	73	73	73	73	73	73	73	73
	97	22	33	22	66	99	99	44	00	01	77	11	99	99	99	99	99	00	00	00	00	00	00	00	00
Carcass ID Number	06	07	06	08	09	08	09	09	05	07	09	09	05	06	07	07	08	05	05	05	06	06	07	07	07
	61	77	70	88	00	09	92	01	77	11	55	66	88	88	00	33	22	11	33	99	33	66	44	55	88
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+							+													
Spinal cord					+							+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X												X								
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma										X		X			X								X		
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, pancreas										X															
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver						X			X		X								X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Adenoma, multiple																									
Lacrimal gland									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urethra		+		+		+																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																						X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	734	
Carcass ID Number	08 1	08 5	08 7	09 4	09 8	10 0	05 2	05 5	06 2	06 4	06 5	06 7	06 9	07 2	07 9	08 6	09 9	05 4	05 6	07 6	08 0	08 3	08 4	09 3	09 7	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X										X				4
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma					X					X		X														7
Alveolar/bronchiolar carcinoma, multiple			X																							1
Carcinoma, metastatic, pancreas																										1
Hepatoblastoma, metastatic, liver										X																1
Hepatocellular carcinoma, metastatic, liver													X													5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X							X													X	4
Adenoma, multiple													X													1
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																X										1
Urethra																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X			X			X												X						5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	734	734	734	
Carcass ID Number	11101	11103	11106	11202	11207	11409	11500	11601	11605	11702	11808	11901	12209	12302	12409	12544	12609	12704	12943	13033	13404	13606	13707	13808		Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine large, colon	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Polyp adenomatous																				X						2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangioma													X													1
Hepatoblastoma									X																	3
Hepatoblastoma, multiple																						X				3
Hepatocellular carcinoma				X				X		X					X		X	X								14
Hepatocellular carcinoma, multiple											X								X							5
Hepatocellular adenoma			X				X		X			X					X	X								13
Hepatocellular adenoma, multiple	X	X		X	X	X		X		X	X		X	X	X	X					X	X	X	X		24
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Mesentery	+						+										+					+	+			10
Hepatoblastoma, metastatic, liver																										1
Osteosarcoma, metastatic, bone																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Capsule, adenoma													X								X					2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma						X									X						X					4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	3 6 7	4 3 1	5 2 1	5 7 3	5 7 6	5 9 6	6 0 4	6 2 5	6 2 6	6 3 1	6 5 3	6 5 4	6 9 1	6 9 9	7 0 8	7 1 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	1 1 5	1 4 6	1 0 7	1 4 0	1 3 1	1 1 0	1 0 6	1 4 1	1 4 3	1 1 9	1 2 2	1 2 8	1 0 2	1 3 8	1 4 2	1 3 5	1 0 3	1 0 4	1 1 7	1 2 4	1 2 5	1 2 6	1 3 0	1 4 7	1 0 8
Genital System																									
Coagulating gland														+											
Hemangioma														X											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+							+			+							+							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Thymus	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+																			
Spinal cord						+																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X						X				X					X			X
Alveolar/bronchiolar adenoma, multiple																		X							
Alveolar/bronchiolar carcinoma															X				X						
Alveolar/bronchiolar carcinoma, multiple														X				X							
Hepatoblastoma, metastatic, liver				X	X																				
Hepatocellular carcinoma, metastatic, liver									X		X	X	X			X									
Osteosarcoma, metastatic, bone			X																						
Bronchus, adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	4	4	4	4	4	4	4	4	
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Total
Carcass ID Number	1	1	1	2	2	4	5	0	0	1	1	2	2	3	3	4	4	0	1	2	3	3	3	3	4	Tissues/
	1	3	6	0	7	9	0	1	5	2	8	1	9	2	9	4	5	9	4	3	3	4	6	7	8	Tumors
Genital System																										
Coagulating gland																										1
Hemangioma																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+																			5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X				X	X				X			X	X						X	X		X	X	15
Alveolar/bronchiolar adenoma, multiple																							X			2
Alveolar/bronchiolar carcinoma							X		X				X										X			6
Alveolar/bronchiolar carcinoma, multiple																										2
Hepatoblastoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, liver				X															X							7
Osteosarcoma, metastatic, bone																										1
Bronchus, adenoma			X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	3 6 7	4 3 1	5 2 1	5 7 3	5 7 6	5 9 6	6 0 4	6 2 5	6 2 6	6 3 1	6 5 3	6 5 4	6 9 1	6 9 9	7 0 8	7 1 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	1 1 5	1 4 6	1 0 7	1 4 0	1 3 1	1 1 0	1 0 6	1 4 1	1 4 3	1 1 9	1 2 2	1 2 8	1 0 2	1 3 8	1 4 2	1 3 5	1 0 3	1 0 4	1 1 7	1 2 4	1 2 5	1 2 6	1 3 0	1 4 7	1 0 8
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X			X	X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant	X	X						X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 1 1	1 1 3	1 1 6	1 2 0	1 2 7	1 4 9	1 5 0	1 0 1	1 0 5	1 1 2	1 1 8	1 2 1	1 2 9	1 3 2	1 3 9	1 4 4	1 4 5	1 4 9	1 0 4	1 1 4	1 2 3	1 3 3	1 3 4	1 3 6	1 3 7	1 4 8	Total Tissues/ Tumors
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X										X																5
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant																											3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	
Carcass ID Number	16 60	17 44	17 75	18 83	18 88	19 00	15 02	15 53	16 64	17 00	17 72	17 73	18 81	18 82	18 84	18 85	19 53	19 55	19 57	19 59	15 51	15 58	17 71	17 76	18 66	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma									X																	1
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma					X																					1
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma				X																X			X			3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X										X						2
Hepatoblastoma		X	X			X				X									X					X		16
Hepatoblastoma, multiple											X															2
Hepatocellular carcinoma						X			X	X													X			11
Hepatocellular carcinoma, multiple							X									X				X	X	X				15
Hepatocellular adenoma		X				X	X		X				X		X	X			X		X		X			15
Hepatocellular adenoma, multiple	X		X	X	X			X		X	X	X		X				X		X		X		X	X	27
Histiocytic sarcoma																										1
Mesentery				+				+																+	+	7
Hepatoblastoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X										X	X													3
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma													X													1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	4 6 9	4 7 6	4 8 9	5 5 8	5 6 3	5 9 7	6 2 3	6 2 7	6 3 7	6 5 2	6 5 9	6 5 9	6 8 9	6 9 1	6 9 2	6 9 4	7 0 2	7 0 6	7 0 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 7 8	1 6 2	1 5 4	1 6 5	1 8 9	1 5 6	1 5 9	1 9 8	1 6 9	1 9 4	1 7 7	1 9 6	1 6 1	1 7 9	1 5 5	1 6 7	1 6 8	1 9 2	1 8 0	1 5 7	1 6 3	1 6 6	1 8 7	2 0 1	2 0 0
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver													X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver													X											
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma												X												
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																		+						
Alveolar/bronchiolar carcinoma, metastatic, lung																		X						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X	X							X								X					
Alveolar/bronchiolar adenoma, multiple																				X				
Alveolar/bronchiolar carcinoma										X														
Alveolar/bronchiolar carcinoma, multiple																		X						
Hepatoblastoma, metastatic, liver									X				X			X								
Hepatocellular carcinoma, metastatic, liver		X			X	X		X		X			X	X			X							X
Histiocytic sarcoma											X													
Mediastinum, hepatoblastoma, metastatic, liver							X								X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 6 0	1 7 4	1 7 5	1 8 3	1 8 8	1 9 0	1 5 2	1 5 3	1 6 4	1 7 0	1 7 2	1 7 3	1 8 1	1 8 2	1 8 4	1 8 5	1 9 3	1 9 5	1 9 7	1 9 9	1 5 1	1 5 8	1 7 1	1 7 6	1 8 6	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis										+																1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma						X																				1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X							X							X	X						8
Alveolar/bronchiolar adenoma, multiple													X				X				X					4
Alveolar/bronchiolar carcinoma			X								X											X				4
Alveolar/bronchiolar carcinoma, multiple													X				X									3
Hepatoblastoma, metastatic, liver		X									X								X							6
Hepatocellular carcinoma, metastatic, liver						X	X									X						X				13
Histiocytic sarcoma																										1
Mediastinum, hepatoblastoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	4 6 9	4 7 6	4 8 9	5 5 8	5 6 3	5 9 7	6 2 3	6 2 7	6 3 7	6 5 2	6 5 9	6 5 9	6 8 9	6 9 1	6 9 2	6 9 4	7 0 2	7 0 6	7 0 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 7 8	1 6 2	1 5 4	1 6 5	1 8 9	1 5 6	1 5 9	1 9 8	1 6 9	1 9 4	1 7 7	1 9 6	1 6 1	1 7 9	1 5 5	1 6 7	1 6 8	1 9 2	1 8 0	1 5 7	1 6 3	1 6 6	1 8 7	1 9 1	2 0 0
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Adenoma, multiple																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	734	734	734	734	
Carcass ID Number	16040	17044	17755	18833	18888	19090	15252	15533	16644	17070	17722	17733	18811	18822	18844	18855	19533	19955	19977	19991	15511	15581	17711	17766	18866	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X											X			X		X		X					6
Adenoma, multiple		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant									X					X												2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Adrenal Cortex: Adenoma				
Overall rate[a]	3/49 (6%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rate[b]	7.1%	8.7%	4.6%	0.0%
Terminal rate[c]	3/31 (10%)	3/38 (8%)	2/34 (6%)	0/31 (0%)
First incidence (days)	729 (T)	659	729 (T)	—[e]
Poly-3 test[d]	P=0.042N	P=0.549	P=0.484N	P=0.113N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	7.1%	10.9%	11.4%	16.0%
Terminal rate	3/31 (10%)	4/38 (11%)	4/34 (12%)	6/31 (19%)
First incidence (days)	729 (T)	721	714	706
Poly-3 test	P=0.151	P=0.404	P=0.375	P=0.169
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	7.1%	10.9%	11.4%	16.0%
Terminal rate	3/31 (10%)	4/38 (11%)	4/34 (12%)	6/31 (19%)
First incidence (days)	729 (T)	721	714	706
Poly-3 test	P=0.151	P=0.404	P=0.375	P=0.169
Liver: Hepatocellular Adenoma				
Overall rate	18/49 (37%)	37/50 (74%)	37/50 (74%)	42/50 (84%)
Adjusted rate	41.6%	78.0%	80.1%	88.7%
Terminal rate	14/31 (45%)	31/38 (82%)	29/34 (85%)	29/31 (94%)
First incidence (days)	596	573	573	469
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	14/49 (29%)	9/50 (18%)	19/50 (38%)	26/50 (52%)
Adjusted rate	31.3%	19.4%	40.7%	54.9%
Terminal rate	6/31 (19%)	6/38 (16%)	10/34 (29%)	14/31 (45%)
First incidence (days)	451	659	573	476
Poly-3 test	P<0.001	P=0.141N	P=0.236	P=0.016
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	28/49 (57%)	41/50 (82%)	42/50 (84%)	47/50 (94%)
Adjusted rate	61.2%	85.8%	88.3%	96.0%
Terminal rate	17/31 (55%)	33/38 (87%)	30/34 (88%)	30/31 (97%)
First incidence (days)	451	573	573	469
Poly-3 test	P<0.001	P=0.004	P<0.001	P<0.001
Liver: Hepatoblastoma				
Overall rate	0/49 (0%)	4/50 (8%)	6/50 (12%)	18/50 (36%)
Adjusted rate	0.0%	8.7%	13.3%	39.1%
Terminal rate	0/31 (0%)	3/38 (8%)	3/34 (9%)	9/31 (29%)
First incidence (days)	—	717	573	469
Poly-3 test	P<0.001	P=0.072	P=0.019	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	14/49 (29%)	11/50 (22%)	23/50 (46%)	37/50 (74%)
Adjusted rate	31.3%	23.7%	48.9%	75.5%
Terminal rate	6/31 (19%)	8/38 (21%)	13/34 (38%)	20/31 (65%)
First incidence (days)	451	659	573	469
Poly-3 test	P<0.001	P=0.281N	P=0.063	P<0.001

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	28/49 (57%)	41/50 (82%)	43/50 (86%)	48/50 (96%)
Adjusted rate	61.2%	85.8%	90.4%	97.4%
Terminal rate	17/31 (55%)	33/38 (87%)	31/34 (91%)	30/31 (97%)
First incidence (days)	451	573	573	469
Poly-3 test	P<0.001	P=0.004	P<0.001	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	7/49 (14%)	5/50 (10%)	17/50 (34%)	12/50 (24%)
Adjusted rate	16.3%	10.8%	38.4%	26.6%
Terminal rate	5/31 (16%)	4/38 (11%)	15/34 (44%)	8/31 (26%)
First incidence (days)	482	596	604	489
Poly-3 test	P=0.019	P=0.326N	P=0.016	P=0.178
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/49 (10%)	8/50 (16%)	8/50 (16%)	7/50 (14%)
Adjusted rate	11.7%	17.3%	18.2%	15.9%
Terminal rate	3/31 (10%)	6/38 (16%)	6/34 (18%)	5/31 (16%)
First incidence (days)	662	691	699	652
Poly-3 test	P=0.436	P=0.329	P=0.294	P=0.400
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	12/49 (24%)	12/50 (24%)	22/50 (44%)	17/50 (34%)
Adjusted rate	27.7%	25.7%	49.4%	37.3%
Terminal rate	8/31 (26%)	9/38 (24%)	18/34 (53%)	11/31 (36%)
First incidence (days)	482	596	604	489
Poly-3 test	P=0.066	P=0.513N	P=0.027	P=0.226
Pancreatic Islets: Adenoma				
Overall rate	0/46 (0%)	3/50 (6%)	4/50 (8%)	3/49 (6%)
Adjusted rate	0.0%	6.5%	9.1%	7.0%
Terminal rate	0/31 (0%)	2/38 (5%)	3/34 (9%)	3/31 (10%)
First incidence (days)	—	721	596	729 (T)
Poly-3 test	P=0.211	P=0.144	P=0.073	P=0.131
Small Intestine (Jejunum): Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	4.4%	0.0%	6.9%
Terminal rate	0/31 (0%)	2/38 (5%)	0/34 (0%)	3/31 (10%)
First incidence (days)	—	729 (T)	—	729 (T)
Poly-3 test	P=0.157	P=0.256	—[f]	P=0.124
Small Intestine (Duodenum, Jejunum): Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	4.4%	0.0%	9.2%
Terminal rate	0/31 (0%)	2/38 (5%)	0/34 (0%)	4/31 (13%)
First incidence (days)	—	729 (T)	—	729 (T)
Poly-3 test	P=0.059	P=0.256	—	P=0.064
Small Intestine (Duodenum, Jejunum, Ileum): Adenomatous Polyp				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	2.4%	6.5%	4.6%	2.3%
Terminal rate	1/31 (3%)	3/38 (8%)	2/34 (6%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	489
Poly-3 test	P=0.371N	P=0.336	P=0.512	P=0.751N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Spleen: Hemangiosarcoma				
Overall rate	2/47 (4%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	4.9%	6.5%	0.0%	0.0%
Terminal rate	2/30 (7%)	3/38 (8%)	0/34 (0%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	—	—
Poly-3 test	P=0.039N	P=0.555	P=0.221N	P=0.222N
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	9.5%	8.7%	0.0%	4.6%
Terminal rate	4/31 (13%)	4/38 (11%)	0/34 (0%)	2/31 (7%)
First incidence (days)	729 (T)	729 (T)	—	729 (T)
Poly-3 test	P=0.127N	P=0.597N	P=0.056N	P=0.323N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.5%	10.9%	4.6%	4.6%
Terminal rate	4/31 (13%)	5/38 (13%)	1/34 (3%)	2/31 (7%)
First incidence (days)	729 (T)	729 (T)	699	729 (T)
Poly-3 test	P=0.138N	P=0.552	P=0.320N	P=0.323N
All Organs: Malignant Lymphoma				
Overall rate	0/50 (0%)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	10.9%	6.6%	4.6%
Terminal rate	0/31 (0%)	5/38 (13%)	0/34 (0%)	2/31 (7%)
First incidence (days)	—	729 (T)	367	729 (T)
Poly-3 test	P=0.518N	P=0.038	P=0.133	P=0.244
All Organs: Benign Neoplasms				
Overall rate	25/50 (50%)	38/50 (76%)	42/50 (84%)	46/50 (92%)
Adjusted rate	56.7%	79.6%	90.4%	94.7%
Terminal rate	19/31 (61%)	31/38 (82%)	32/34 (94%)	31/31 (100%)
First incidence (days)	482	573	573	469
Poly-3 test	P<0.001	P=0.012	P<0.001	P<0.001
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	28/50 (56%)	32/50 (64%)	43/50 (86%)
Adjusted rate	50.9%	59.5%	64.6%	87.2%
Terminal rate	12/31 (39%)	22/38 (58%)	17/34 (50%)	25/31 (81%)
First incidence (days)	451	596	367	469
Poly-3 test	P<0.001	P=0.267	P=0.125	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	37/50 (74%)	44/50 (88%)	49/50 (98%)	50/50 (100%)
Adjusted rate	79.1%	91.6%	98.0%	100.0%
Terminal rate	23/31 (74%)	35/38 (92%)	33/34 (97%)	31/31 (100%)
First incidence (days)	451	573	367	469
Poly-3 test	P<0.001	P=0.067	P=0.002	P<0.001

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreatic islets, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE C4a
Historical Incidence of Neoplasms in the Liver of Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma	Hepatoblastoma
Historical Incidence: Drinking Water Studies				
Dibromoacetic acid	18/49	14/49	28/49	0/49
Dipropylene glycol	17/50	14/50	29/50	0/50
Sodium chlorate	30/48	20/48	41/48	6/48
Sodium nitrite	19/50	9/50	24/50	5/50
Overall Historical Incidence: Drinking Water Studies				
Total (%)	84/197 (42.6%)	57/197 (28.9%)	122/197 (61.9%)	11/197 (5.6%)
Mean ± standard deviation	34.3% ± 22.3%	23.3% ± 15.5%	49.7% ± 31.1%	4.5% ± 6.2%
Range	34%-63%	18%-42%	48%-85%	0%-13%
Overall Historical Incidence				
Total (%)	490/1,506 (32.5%)	344/1,506 (22.8%)	745/1,506 (49.5%)	22/1,506 (1.5%)
Mean ± standard deviation	32.6% ± 12.7%	22.9% ± 10.0%	49.5% ± 17.8%	1.5% ± 3.1%
Range	12%-63%	8%-46%	20%-85%	0%-13%

[a] Data as of January 26, 2005

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Drinking Water Studies			
Dibromoacetic acid	7/49	5/49	12/49
Dipropylene glycol	3/50	3/50	6/50
Sodium chlorate	6/50	4/50	10/50
Sodium nitrite	10/50	4/50	13/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	26/199 (13.1%)	16/199 (8.0%)	41/199 (20.6%)
Mean ± standard deviation	10.5% ± 7.7%	6.4% ± 3.9%	16.5% ± 10.7%
Range	6%-20%	6%-10%	12%-26%
Overall Historical Incidence			
Total (%)	258/1,507 (17.1%)	151/1,507 (10.0%)	385/1,507 (25.6%)
Mean ± standard deviation	16.7% ± 7.3%	9.9% ± 5.0%	25.1% ± 9.4%
Range	4%-28%	4%-24%	12%-44%

[a] Data as of January 26, 2005

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Disposition Summary								
Animals initially in study	50		50		50		50	
Early deaths								
Other	1							
Moribund	4		6		3		6	
Natural deaths	14		6		13		13	
Survivors								
Terminal sacrifice	31		38		34		31	
Animals examined microscopically	49		50		50		50	
Alimentary System								
Intestine large, cecum	(43)		(49)		(48)		(46)	
Edema	2	(5%)	2	(4%)	3	(6%)	1	(2%)
Hyperplasia, lymphoid					1	(2%)		
Intestine small, duodenum	(42)		(50)		(46)		(48)	
Hyperplasia, lymphoid			1	(2%)				
Intestine small, jejunum	(44)		(49)		(46)		(45)	
Hyperplasia, lymphoid					2	(4%)	2	(4%)
Liver	(49)		(50)		(50)		(50)	
Angiectasis					1	(2%)		
Basophilic focus	2	(4%)			1	(2%)	2	(4%)
Clear cell focus	10	(20%)	13	(26%)	23	(46%)	13	(26%)
Congestion	1	(2%)						
Cyst			1	(2%)			1	(2%)
Eosinophilic focus	15	(31%)	10	(20%)	15	(30%)	17	(34%)
Hematopoietic cell proliferation							1	(2%)
Hemorrhage	1	(2%)						
Hepatodiaphragmatic nodule			1	(2%)				
Infarct	1	(2%)			1	(2%)		
Infiltration cellular, mixed cell	2	(4%)	4	(8%)	2	(4%)	2	(4%)
Mixed cell focus	3	(6%)	7	(14%)	8	(16%)	4	(8%)
Necrosis, focal	8	(16%)	7	(14%)	3	(6%)	5	(10%)
Tension lipidosis			1	(2%)	1	(2%)	2	(4%)
Bile duct, cyst					1	(2%)		
Bile duct, cyst multilocular					1	(2%)		
Centrilobular, necrosis	4	(8%)	4	(8%)			5	(10%)
Hepatocyte, vacuolization cytoplasmic	8	(16%)	9	(18%)	4	(8%)	10	(20%)
Kupffer cell, pigmentation	1	(2%)	1	(2%)	1	(2%)	1	(2%)
Mesentery	(7)		(7)		(10)		(7)	
Inflammation, chronic					1	(10%)		
Fat, necrosis	5	(71%)	6	(86%)	7	(70%)	4	(57%)
Pancreas	(46)		(50)		(50)		(49)	
Necrosis			1	(2%)				
Acinus, cytoplasmic alteration	2	(4%)	2	(4%)	2	(4%)		
Salivary glands	(49)		(50)		(50)		(50)	
Atrophy	1	(2%)					2	(4%)
Hyperplasia, lymphoid	3	(6%)	4	(8%)	6	(12%)	1	(2%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Alimentary System (continued)								
Stomach, forestomach	(49)		(50)		(50)		(50)	
Diverticulum			2	(4%)	1	(2%)		
Erosion	1	(2%)			1	(2%)	2	(4%)
Inflammation, chronic	3	(6%)	1	(2%)	3	(6%)	6	(12%)
Ulcer	2	(4%)	2	(4%)	2	(4%)	2	(4%)
Epithelium, hyperplasia	4	(8%)	3	(6%)	4	(8%)	7	(14%)
Epithelium, hyperplasia, focal					1	(2%)	1	(2%)
Stomach, glandular	(47)		(50)		(50)		(50)	
Erosion	2	(4%)	2	(4%)	1	(2%)		
Glands, hyperplasia			1	(2%)				
Tooth	(5)		(6)					
Malformation	5	(100%)	6	(100%)				
Cardiovascular System								
Heart	(49)		(50)		(50)		(50)	
Cardiomyopathy	1	(2%)	1	(2%)				
Inflammation, chronic	1	(2%)						
Mineralization	3	(6%)			2	(4%)	1	(2%)
Myocardium, necrosis			1	(2%)				
Endocrine System								
Adrenal cortex	(49)		(50)		(50)		(50)	
Accessory adrenal cortical nodule	7	(14%)	5	(10%)	4	(8%)	6	(12%)
Hyperplasia, focal	4	(8%)	7	(14%)	5	(10%)	1	(2%)
Hypertrophy	1	(2%)					1	(2%)
Hypertrophy, focal	12	(24%)	11	(22%)	13	(26%)	6	(12%)
Capsule, hyperplasia	7	(14%)	4	(8%)	1	(2%)	5	(10%)
Adrenal medulla	(49)		(50)		(50)		(50)	
Hyperplasia	1	(2%)	1	(2%)			1	(2%)
Islets, pancreatic	(46)		(50)		(50)		(49)	
Atrophy							1	(2%)
Hyperplasia	34	(74%)	32	(64%)	26	(52%)	13	(27%)
Parathyroid gland	(45)		(47)		(49)		(47)	
Cyst			2	(4%)	3	(6%)	4	(9%)
Pituitary gland	(45)		(50)		(48)		(48)	
Pars distalis, cyst	7	(16%)	7	(14%)	7	(15%)	5	(10%)
Pars distalis, hyperplasia, focal	1	(2%)			1	(2%)		
Thyroid gland	(48)		(50)		(50)		(50)	
Degeneration, cystic	5	(10%)	8	(16%)	3	(6%)	6	(12%)
Follicular cell, hyperplasia	3	(6%)						
General Body System								
None								
Genital System								
Epididymis	(49)		(50)		(50)		(50)	
Atypia cellular	5	(10%)	4	(8%)	2	(4%)	6	(12%)
Granuloma sperm	1	(2%)	2	(4%)	2	(4%)	2	(4%)
Spermatocele	1	(2%)					1	(2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Genital System (continued)								
Preputial gland	(49)		(50)		(50)		(50)	
Cyst	25	(51%)	26	(52%)	33	(66%)	33	(66%)
Inflammation, chronic	21	(43%)	30	(60%)	24	(48%)	28	(56%)
Prostate	(48)		(50)		(50)		(49)	
Inflammation, chronic			4	(8%)			1	(2%)
Seminal vesicle	(49)		(50)		(50)		(50)	
Degeneration	3	(6%)	5	(10%)	1	(2%)		
Inflammation, chronic	1	(2%)						
Testes	(49)		(50)		(50)		(50)	
Germinal epithelium, atrophy	9	(18%)	4	(8%)	4	(8%)	8	(16%)
Hematopoietic System								
Bone marrow	(47)		(50)		(50)		(50)	
Angiectasis							1	(2%)
Depletion cellular	1	(2%)						
Hyperplasia	22	(47%)	22	(44%)	28	(56%)	32	(64%)
Lymph node	(1)		(2)		(5)		(1)	
Bronchial, hyperplasia, lymphoid					1	(20%)		
Iliac, ectasia			1	(50%)				
Inguinal, hyperplasia, lymphoid					1	(20%)		
Inguinal, pigmentation			1	(50%)				
Mediastinal, hyperplasia, lymphoid	1	(100%)			1	(20%)		
Mediastinal, pigmentation							1	(100%)
Pancreatic, hyperplasia, lymphoid					1	(20%)		
Lymph node, mandibular	(48)		(50)		(48)		(48)	
Atrophy	5	(10%)	2	(4%)	3	(6%)	7	(15%)
Hematopoietic cell proliferation	1	(2%)						
Hemorrhage	1	(2%)			1	(2%)		
Hyperplasia, lymphoid	15	(31%)	14	(28%)	6	(13%)	7	(15%)
Pigmentation	7	(15%)	8	(16%)	1	(2%)	7	(15%)
Lymph node, mesenteric	(46)		(49)		(49)		(47)	
Atrophy	4	(9%)	2	(4%)	1	(2%)	9	(19%)
Hematopoietic cell proliferation	1	(2%)	1	(2%)	3	(6%)	3	(6%)
Hemorrhage	8	(17%)	5	(10%)	9	(18%)	7	(15%)
Hyperplasia, lymphoid	2	(4%)	8	(16%)	3	(6%)	6	(13%)
Hyperplasia, plasma cell					1	(2%)		
Spleen	(47)		(50)		(50)		(50)	
Angiectasis							1	(2%)
Hematopoietic cell proliferation	18	(38%)	20	(40%)	28	(56%)	38	(76%)
Pigmentation			1	(2%)	1	(2%)	1	(2%)
Lymphoid follicle, atrophy	4	(9%)	7	(14%)	3	(6%)	8	(16%)
Lymphoid follicle, hyperplasia	3	(6%)	6	(12%)	6	(12%)	6	(12%)
Thymus	(42)		(45)		(46)		(47)	
Atrophy	14	(33%)	16	(36%)	12	(26%)	22	(47%)
Hyperplasia, lymphoid			1	(2%)	1	(2%)	1	(2%)
Integumentary System								
Skin	(49)		(50)		(50)		(50)	
Cyst epithelial inclusion			2	(4%)				
Ulcer	3	(6%)	2	(4%)			3	(6%)
Epidermis, hyperplasia	3	(6%)	2	(4%)			3	(6%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Hyperostosis		1 (2%)		
Cranium, hyperostosis	1 (2%)			1 (2%)
Skeletal muscle	(1)	(1)		(1)
Atrophy		1 (100%)		
Nervous System				
Peripheral nerve	(2)	(2)	(1)	
Atrophy		1 (50%)	1 (100%)	
Spinal cord	(2)	(2)	(1)	
Gliosis	1 (50%)			
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Edema	2 (4%)		1 (2%)	2 (4%)
Hemorrhage	2 (4%)			4 (8%)
Hyperplasia, lymphoid	3 (6%)		1 (2%)	
Infiltration cellular, histiocyte	2 (4%)	6 (12%)	3 (6%)	6 (12%)
Metaplasia, osseous	1 (2%)	2 (4%)		1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	6 (12%)	6 (12%)	7 (14%)
Bronchiole, hyperplasia				1 (2%)
Nose	(48)	(50)	(50)	(50)
Foreign body			1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	3 (6%)	
Special Senses System				
Eye	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		
Cataract		1 (2%)	1 (2%)	5 (10%)
Inflammation, chronic			2 (4%)	2 (4%)
Bilateral, cataract				1 (2%)
Cornea, hyperplasia			1 (2%)	1 (2%)
Harderian gland	(49)	(50)	(50)	(50)
Cyst		1 (2%)		
Hyperplasia, focal	5 (10%)	1 (2%)	1 (2%)	1 (2%)
Lacrimal gland		(1)		
Cyst		1 (100%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Urinary System								
Kidney	(49)		(50)		(50)		(50)	
Cyst	9	(18%)	13	(26%)	14	(28%)	11	(22%)
Hydronephrosis	4	(8%)	2	(4%)			4	(8%)
Hyperplasia, lymphoid	5	(10%)	5	(10%)	6	(12%)	5	(10%)
Infarct	3	(6%)	7	(14%)	4	(8%)	5	(10%)
Inflammation, suppurative			1	(2%)			1	(2%)
Metaplasia, osseous	6	(12%)	3	(6%)	2	(4%)	2	(4%)
Nephropathy	36	(73%)	44	(88%)	42	(84%)	39	(78%)
Papilla, necrosis							1	(2%)
Renal tubule, accumulation, hyaline droplet					1	(2%)		
Renal tubule, dilatation	1	(2%)	3	(6%)			1	(2%)
Renal tubule, hyperplasia	1	(2%)	1	(2%)	1	(2%)	3	(6%)
Renal tubule, necrosis	1	(2%)						
Renal tubule, pigmentation	1	(2%)	3	(6%)	2	(4%)	7	(14%)
Transitional epithelium, hyperplasia					1	(2%)		
Urethra			(3)					
Angiectasis			3	(100%)				
Inflammation, chronic active			3	(100%)				
Urinary bladder	(49)		(50)		(50)		(49)	
Edema					1	(2%)		
Hemorrhage			1	(2%)				
Hyperplasia, lymphoid			1	(2%)	1	(2%)		
Inflammation, chronic							1	(2%)
Transitional epithelium, hyperplasia					1	(2%)	1	(2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF DIBROMOACETIC ACID

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	2	2	5	7
Natural deaths	10	13	13	11
Survivors				
Died last week of study			1	
Terminal sacrifice	38	35	31	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(47)	(46)	(49)	(46)
Intestine small, duodenum	(46)	(48)	(48)	(45)
Polyp adenomatous		2 (4%)		
Intestine small, jejunum	(46)	(47)	(49)	(43)
Carcinoma				1 (2%)
Sarcoma, metastatic, skin		1 (2%)		
Intestine small, ileum	(45)	(47)	(47)	(46)
Fibrosarcoma, metastatic, tissue NOS				1 (2%)
Liver	(49)	(50)	(50)	(49)
Hemangioma	1 (2%)		1 (2%)	
Hemangiosarcoma	1 (2%)	1 (2%)	2 (4%)	
Hepatoblastoma	1 (2%)		1 (2%)	
Hepatoblastoma, multiple				1 (2%)
Hepatocellular carcinoma	2 (4%)	2 (4%)	7 (14%)	5 (10%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)	5 (10%)	3 (6%)
Hepatocellular adenoma	8 (16%)	12 (24%)	9 (18%)	9 (18%)
Hepatocellular adenoma, multiple	11 (22%)	14 (28%)	23 (46%)	26 (53%)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Ito cell tumor malignant				1 (2%)
Sarcoma	1 (2%)			
Sarcoma, metastatic, skin		1 (2%)		
Mesentery	(28)	(20)	(16)	(19)
Hemangioma	1 (4%)			
Hemangiosarcoma			1 (6%)	1 (5%)
Leiomyosarcoma			1 (6%)	
Sarcoma	1 (4%)			
Sarcoma, metastatic, pancreas			1 (6%)	
Sarcoma, metastatic, skin		1 (5%)		
Schwannoma malignant, metastatic, skin		1 (5%)		
Oral mucosa		(1)		
Squamous cell carcinoma		1 (100%)		
Pancreas	(49)	(49)	(49)	(47)
Histiocytic sarcoma				1 (2%)
Schwannoma malignant, metastatic, skin		1 (2%)		
Acinus, carcinoma				1 (2%)
Acinus, sarcoma			1 (2%)	
Salivary glands	(50)	(49)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)	1 (2%)
Squamous cell papilloma	1 (2%)	1 (2%)	2 (4%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(50)	(49)
Carcinoma	1 (2%)			
Schwannoma malignant, metastatic, skin		1 (2%)		
Serosa, sarcoma, metastatic, skin		1 (2%)		
Tongue	(2)			
Squamous cell carcinoma	1 (50%)			
Squamous cell papilloma	1 (50%)			
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Leiomyosarcoma, metastatic, mesentery			1 (2%)	
Sarcoma, metastatic, pancreas			1 (2%)	
Capsule, adenoma			1 (2%)	
Extra adrenal tissue, sarcoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma benign	1 (2%)		1 (2%)	1 (2%)
Islets, pancreatic	(49)	(49)	(49)	(46)
Adenoma	1 (2%)		2 (4%)	2 (4%)
Carcinoma			1 (2%)	
Pituitary gland	(47)	(49)	(49)	(49)
Pars distalis, adenoma	2 (4%)	4 (8%)		1 (2%)
Pars intermedia, adenoma	1 (2%)		2 (4%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	3 (6%)			
General Body System				
Tissue NOS				(2)
Fibrosarcoma				1 (50%)
Schwannoma malignant				1 (50%)
Genital System				
Ovary	(49)	(47)	(47)	(49)
Cystadenoma		2 (4%)	1 (2%)	
Hemangioma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Leiomyoma				1 (2%)
Polyp stromal	1 (2%)	1 (2%)		
Sarcoma stromal				1 (2%)
Cervix, carcinoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Lymph node	(12)	(13)	(11)	(8)
Fibrosarcoma, metastatic, skin		1 (8%)		
Iliac, osteosarcoma, metastatic, bone				1 (13%)
Iliac, sarcoma, metastatic, skin	1 (8%)	1 (8%)		
Inguinal, fibrosarcoma, metastatic, skin		1 (8%)		
Mediastinal, neurofibrosarcoma, metastatic, skin		1 (8%)		
Mediastinal, sarcoma, metastatic, skin				1 (13%)
Pancreatic, carcinoma, metastatic, pancreas				1 (13%)
Pancreatic, leiomyosarcoma, metastatic, mesentery			1 (9%)	
Renal, leiomyosarcoma, metastatic, mesentery			1 (9%)	
Lymph node, mandibular	(48)	(49)	(47)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Lymph node, mesenteric	(49)	(49)	(48)	(45)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Spleen	(50)	(50)	(50)	(48)
Histiocytic sarcoma		1 (2%)		1 (2%)
Thymus	(44)	(47)	(47)	(48)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)	1 (2%)	
Fibroadenoma		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma				1 (2%)
Squamous cell carcinoma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrous histiocytoma	3 (6%)			
Subcutaneous tissue, hemangioma		1 (2%)		1 (2%)
Subcutaneous tissue, hemangiopericytoma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, neurofibroma				1 (2%)
Subcutaneous tissue, neurofibrosarcoma		1 (2%)		
Subcutaneous tissue, osteosarcoma, metastatic, bone				1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Subcutaneous tissue, sarcoma, metastatic, tissue NOS	1 (2%)			
Subcutaneous tissue, schwannoma malignant		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)	1 (2%)	1 (2%)
Skeletal muscle	(3)	(4)	(2)	(5)
Carcinoma, metastatic, harderian gland		1 (25%)		
Fibrosarcoma, metastatic, skin			1 (50%)	
Hemangiosarcoma				1 (20%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Musculoskeletal System (continued)								
Skeletal muscle (continued)	(3)		(4)		(2)		(5)	
Hepatocellular carcinoma, metastatic, liver	1	(33%)						
Rhabdomyosarcoma							1	(20%)
Sarcoma	1	(33%)	1	(25%)			2	(40%)
Sarcoma, metastatic, pancreas					1	(50%)		
Sarcoma, metastatic, skin	1	(33%)						
Schwannoma malignant, metastatic, skin			1	(25%)				
Nervous System								
None								
Respiratory System								
Lung	(50)		(50)		(50)		(50)	
Alveolar/bronchiolar adenoma	1	(2%)	3	(6%)	3	(6%)	6	(12%)
Alveolar/bronchiolar carcinoma	1	(2%)	2	(4%)	2	(4%)	2	(4%)
Carcinoma, metastatic, harderian gland			1	(2%)				
Carcinoma, metastatic, uterus					1	(2%)		
Fibrosarcoma, metastatic, skin	1	(2%)	2	(4%)	1	(2%)	1	(2%)
Hepatocellular carcinoma, metastatic, liver	3	(6%)	1	(2%)	3	(6%)	4	(8%)
Histiocytic sarcoma			1	(2%)				
Neurofibrosarcoma			1	(2%)				
Osteosarcoma, metastatic, bone							1	(2%)
Sarcoma, metastatic, skin	1	(2%)	1	(2%)			1	(2%)
Nose	(50)		(50)		(50)		(50)	
Carcinoma, metastatic, harderian gland			1	(2%)				
Special Senses System								
Eye	(50)		(50)		(50)		(50)	
Carcinoma, metastatic, harderian gland			1	(2%)				
Harderian gland	(49)		(50)		(50)		(50)	
Adenoma	9	(18%)	4	(8%)	6	(12%)	8	(16%)
Adenoma, multiple					2	(4%)		
Carcinoma	1	(2%)	2	(4%)	2	(4%)	1	(2%)
Urinary System								
Kidney	(49)		(50)		(50)		(49)	
Urinary bladder	(50)		(49)		(50)		(49)	
Fibrosarcoma, metastatic, tissue NOS							1	(2%)
Leiomyosarcoma, metastatic, mesentery					1	(2%)		
Systemic Lesions								
Multiple organs[b]	(50)		(50)		(50)		(50)	
Histiocytic sarcoma			1	(2%)	1	(2%)	1	(2%)
Lymphoma malignant	27	(54%)	24	(48%)	17	(34%)	14	(28%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	43	46	48
Total primary neoplasms	88	93	102	104
Total animals with benign neoplasms	29	33	41	38
Total benign neoplasms	43	46	54	56
Total animals with malignant neoplasms	36	37	34	31
Total malignant neoplasms	45	47	48	48
Total animals with metastatic neoplasms	5	7	7	10
Total metastatic neoplasms	12	20	13	13

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	4 7 4	5 1 7	5 5 5	5 6 3	5 9 1	6 2 1	6 5 3	6 5 8	7 1 0	7 1 4	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 4 9	2 2 8	2 1 7	2 3 6	2 3 9	2 0 4	2 2 2	2 5 0	2 4 3	2 0 3	2 2 0	2 1 0	2 3 1	2 3 2	2 3 3	2 3 4	2 3 5	2 1 1	2 1 2	2 1 3	2 1 4	2 1 5	2 1 6	2 1 8	2 1 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	M	+	A	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma							X																		
Hepatoblastoma																						X			
Hepatocellular carcinoma								X																	
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma							X								X			X	X						
Hepatocellular adenoma, multiple													X				X				X	X	X		
Sarcoma			X																						
Mesentery	+	+	+	+		+	+		+	+		+	+		+		+		+	+	+		+		+
Hemangioma																									
Sarcoma			X																						
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Tongue				+																					
Squamous cell carcinoma																									
Squamous cell papilloma				X																					
Cardiovascular System																									
Blood vessel																	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, sarcoma						X																			
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 1	2 2 3	2 2 4	2 2 5	2 4 6	2 4 7	2 4 8	2 3 7	2 3 8	2 4 0	2 0 1	2 0 2	2 0 5	2 0 6	2 0 7	2 0 8	2 0 9	2 2 6	2 2 7	2 2 9	2 3 0	2 4 1	2 4 2	2 4 4	2 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																	X									1
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma										X																2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X	X		X														X								8
Hepatocellular adenoma, multiple			X					X	X				X						X	X						11
Sarcoma																										1
Mesentery	+	+					+	+		+	+		+				+	+		+				+		28
Hemangioma													X													1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																		X								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Tongue											+															2
Squamous cell carcinoma											X															1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Extra adrenal tissue, sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	4 7 4	5 1 7	5 5 5	5 6 3	5 9 1	6 2 1	6 5 3	6 5 8	7 1 0	7 1 4	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 4 9	2 2 8	2 1 7	2 3 6	2 3 9	2 0 4	2 2 2	2 5 0	2 4 3	2 0 3	2 2 0	2 1 0	2 3 1	2 3 2	2 3 3	2 3 4	2 3 5	2 1 1	2 1 2	2 1 3	2 1 4	2 1 5	2 1 6	2 1 8	2 1 9
Endocrine System (continued)																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X					X									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X															
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Polyp stromal																		X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+				+					+			+	+			+			+		+	
Iliac, sarcoma, metastatic, skin															X										
Lymph node, mandibular	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	+	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, fibrous histiocytoma															X		X								
Subcutaneous tissue, sarcoma															X										
Subcutaneous tissue, sarcoma, metastatic, tissue NOS						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+					+		+										
Hepatocellular carcinoma, metastatic, liver								X																	
Sarcoma													X												
Sarcoma, metastatic, skin															X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	2 2 1	2 2 3	2 2 4	2 2 5	2 4 6	2 4 7	2 4 8	2 3 7	2 3 8	2 4 0	2 0 1	2 0 2	2 0 5	2 0 6	2 0 7	2 0 8	2 0 9	2 2 6	2 2 7	2 2 9	2 3 0	2 4 1	2 4 2	2 4 4	2 4 5	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Pars distalis, adenoma																										2
Pars intermedia, adenoma																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X									X													3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma	X																									1
Polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+															+								+		12
Iliac, sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocellular carcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, fibrous histiocytoma											X															3
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, sarcoma, metastatic, tissue NOS																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Hepatocellular carcinoma, metastatic, liver																										1
Sarcoma																										1
Sarcoma, metastatic, skin																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	47 14	51 77	55 55	56 53	59 51	62 61	65 63	65 88	71 10	71 14	72 20	72 33	73 34	73 34	73 34	73 34	73 44	73 45	73 55	73 55	73 55	73 55	73 55	73 55	73 55
Carcass ID Number	24 19	22 08	21 07	23 36	23 39	20 04	22 02	25 20	24 03	20 03	22 00	21 00	23 01	23 02	23 03	23 04	23 05	11 01	11 02	11 03	11 04	11 05	11 06	11 08	11 09
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin									X																
Hepatocellular carcinoma, metastatic, liver								X	X																
Sarcoma, metastatic, skin															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X			X			X		X								X				
Carcinoma																X									
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X											X	X			X	X		X	X	X	X		X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 0 mg/L

Number of Days on Study	735	735	735	735	735	735	735	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	22021	22023	22024	22025	24046	24047	24048	23037	23038	24040	20001	20002	20005	20006	20007	20008	20009	22026	22027	22029	23030	24041	24042	24044	24045	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																						X				1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver										X																3
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma						X							X			X				X						9
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X	X	X	X	X	X	X	X	X				X	X		X	X	X		X	X			X		27

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	3 8 3	4 8 7	4 9 0	5 8 4	6 0 1	6 1 5	6 5 9	6 8 2	6 9 4	6 9 7	7 0 6	7 1 0	7 1 5	7 2 1	7 2 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 5 6	2 7 0	2 6 3	2 9 6	2 9 7	2 6 2	2 7 2	2 9 2	2 8 3	2 8 1	2 8 4	2 5 4	2 5 7	2 9 4	2 7 5	2 5 1	2 5 2	2 5 3	2 5 5	2 7 6	2 7 7	2 7 8	2 7 9	2 8 0	2 9 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Gallbladder	A	A	+	A	A	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	A	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous							X																		
Intestine small, jejunum	+	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin												X													
Intestine small, ileum	+	+	+	M	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma									X			X	X						X			X		X	
Hepatocellular adenoma, multiple														X			X	X					X		
Histiocytic sarcoma														X											
Sarcoma, metastatic, skin												X													
Mesentery				+		+	+	+	+	+		+		+			+	+	+						
Sarcoma, metastatic, skin												X													
Schwannoma malignant, metastatic, skin										X															
Oral mucosa																					+				
Squamous cell carcinoma																					X				
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin										X															
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin										X															
Serosa, sarcoma, metastatic, skin												X													
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29099	30000	29058	29059	29060	29061	29064	29065	29066	29067	29068	29069	29071	29073	29074	29082	29085	29086	29087	29088	29089	29090	29091	29093	29095	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous													X													2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, skin																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Hepatocellular carcinoma																					X				X	2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X		X		X												X			X				X		12
Hepatocellular adenoma, multiple				X		X		X		X		X		X	X	X			X			X				14
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Mesentery			+		+	+					+	+	+		+									+	+	20
Sarcoma, metastatic, skin																										1
Schwannoma malignant, metastatic, skin																										1
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Serosa, sarcoma, metastatic, skin																										1
Cardiovascular System																										
Blood vessel								+																		1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma								X																		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	3 8 3	4 8 7	4 9 0	5 8 4	6 0 1	6 1 5	6 5 9	6 8 2	6 9 4	6 9 7	7 0 6	7 1 0	7 1 5	7 2 1	7 2 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 5 6	2 7 0	2 6 3	2 9 6	2 9 7	2 6 2	2 7 2	2 9 2	2 8 3	2 8 1	2 8 4	2 5 4	2 5 7	2 9 4	2 7 5	2 5 1	2 5 2	2 5 3	2 5 5	2 7 6	2 7 7	2 7 8	2 7 9	2 8 0	2 9 8
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X								X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+		+					+	+			+			+			+							+
Fibrosarcoma, metastatic, skin			X																						
Iliac, sarcoma, metastatic, skin												X													
Inguinal, fibrosarcoma, metastatic, skin			X																						
Mediastinal, neurofibrosarcoma, metastatic, skin	X																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Thymus	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																						X			
Subcutaneous tissue, fibrosarcoma			X								X														
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiopericytoma																									
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, neurofibrosarcoma	X																								
Subcutaneous tissue, sarcoma												X													
Subcutaneous tissue, schwannoma malignant										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29099	30030	25808	25909	26060	26061	26064	26065	26066	26067	26068	26069	27011	27013	27014	28022	28025	28026	28027	28028	28029	29030	29031	29033	29035	Total Tissues/ Tumors
Endocrine System (continued)																											
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X																						4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Cystadenoma					X																					2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Lymph node		+										+						+		+		+				13
Fibrosarcoma, metastatic, skin																										1
Iliac, sarcoma, metastatic, skin																										1
Inguinal, fibrosarcoma, metastatic, skin																										1
Mediastinal, neurofibrosarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								1
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, hemangioma		X																								1
Subcutaneous tissue, hemangiopericytoma																	X									1
Subcutaneous tissue, hemangiosarcoma																X										1
Subcutaneous tissue, neurofibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	383	487	490	584	601	615	659	682	694	697	706	710	715	721	724	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	25 56	27 70	26 63	29 66	29 67	26 62	27 22	29 22	28 83	28 81	28 84	25 44	25 57	29 44	27 45	25 51	25 52	25 53	25 55	27 56	27 77	27 78	27 79	28 80	29 08
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																					X				
Skeletal muscle						+				+						+									
Carcinoma, metastatic, harderian gland						X																			
Sarcoma																X									
Schwannoma malignant, metastatic, skin										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																		X				
Alveolar/bronchiolar carcinoma									X														X		
Carcinoma, metastatic, harderian gland						X																			
Fibrosarcoma, metastatic, skin			X								X														
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma														X											
Neurofibrosarcoma	X																								
Sarcoma, metastatic, skin												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland						X																			
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X				X																			
Carcinoma						X			X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymphoma malignant			X				X								X	X	X	X	X			X	X	X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 50 mg/L

Number of Days on Study	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	29099	30010	25808	25909	26060	26061	26064	26065	26066	26067	26068	26069	27071	27073	27074	28082	28085	28086	28087	28088	28089	29090	29091	29093	29095	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																			+							4
Carcinoma, metastatic, harderian gland																										1
Sarcoma																										1
Schwannoma malignant, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Peripheral nerve																			+							1
Spinal cord																			+							1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						3
Alveolar/bronchiolar carcinoma																										2
Carcinoma, metastatic, harderian gland																										1
Fibrosarcoma, metastatic, skin																										2
Hepatocellular carcinoma, metastatic, liver																									X	1
Histiocytic sarcoma																										1
Neurofibrosarcoma																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear								+																		1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X			X				4
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant			X	X		X	X			X		X		X	X		X	X		X		X		X		24

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	32 4	32 5	33 6	33 8	34 0	34 1	34 2	34 3	34 4	34 5	30 3	30 4	30 5	30 6	30 7	30 9	31 6	31 7	31 8	31 9	33 0	34 6	34 8	34 9	35 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										2
Hepatoblastoma																										1
Hepatocellular carcinoma		X					X									X	X	X							X	7
Hepatocellular carcinoma, multiple			X											X												5
Hepatocellular adenoma			X				X								X			X	X						X	9
Hepatocellular adenoma, multiple	X	X		X	X	X				X	X	X	X	X						X	X	X	X	X		23
Histiocytic sarcoma																										1
Mesentery	+	+												+		+				+		+				16
Hemangiosarcoma																										1
Leiomyosarcoma																										1
Sarcoma, metastatic, pancreas																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																	X									1
Squamous cell papilloma											X															2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, pancreas																										1
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X																								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X							2
Carcinoma																										1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	4 7 9	5 0 7	5 5 3	5 7 3	6 1 7	6 1 8	6 2 2	6 2 9	6 3 4	6 4 3	6 5 9	6 6 8	6 8 0	6 9 2	7 0 1	7 1 2	7 1 8	7 2 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6
Carcass ID Number	3 0 2	3 3 9	3 2 9	3 3 7	3 0 1	3 3 4	3 1 1	3 1 4	3 2 8	3 2 2	3 1 2	3 3 2	3 2 0	3 2 7	3 1 5	3 4 7	3 2 6	3 2 0	3 1 0	3 1 3	3 3 1	3 3 3	3 3 5	3 2 1	3 2 3
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars intermedia, adenoma						X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Cervix, carcinoma															X										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+	+	+				M	+	+											+
Pancreatic, leiomyosarcoma, metastatic, mesentery													X												
Renal, leiomyosarcoma, metastatic, mesentery													X												
Lymph node, mandibular	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Subcutaneous tissue, sarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																			X						
Skeletal muscle				+								+													
Fibrosarcoma, metastatic, skin				X																					
Sarcoma, metastatic, pancreas												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																	+								
Spinal cord																	+								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 2 4	3 2 5	3 3 6	3 3 8	3 4 0	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	3 0 3	3 0 4	3 0 5	3 0 6	3 0 7	3 0 9	3 1 6	3 1 7	3 1 8	3 1 9	3 3 0	3 4 6	3 4 8	3 4 9	3 5 0	Total Tissues/ Tumors
Endocrine System (continued)																										
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars intermedia, adenoma																		X								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	I	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma	X																									1
Hemangioma																						X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Cervix, carcinoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+						+									+	+						+			11
Pancreatic, leiomyosarcoma, metastatic, mesentery																										1
Renal, leiomyosarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma							X																			2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										2
Fibrosarcoma, metastatic, skin																										1
Sarcoma, metastatic, pancreas																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	479	507	553	573	617	618	622	629	634	643	659	668	680	692	701	712	718	724	735	755	755	755	755	763	763
Carcass ID Number	30202	30329	30229	30337	30401	30314	31011	31144	31228	32212	32122	32322	32020	32207	32151	32147	32266	32208	32010	32113	32133	32335	32251	32261	32323
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X													X									
Alveolar/bronchiolar carcinoma							X																		
Carcinoma, metastatic, uterus															X										
Fibrosarcoma, metastatic, skin				X																					
Hepatocellular carcinoma, metastatic, liver																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X	X									X								
Adenoma, multiple																									
Carcinoma														X										X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, mesentery													X												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant						X		X						X		X	X		X					X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 500 mg/L

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	32 4	32 5	33 6	33 8	34 0	34 1	34 2	34 3	34 4	34 5	00 3	00 4	00 5	00 6	00 7	00 9	11 6	11 7	11 8	11 9	13 0	34 6	34 8	34 9	35 0	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				3
Alveolar/bronchiolar carcinoma																	X									2
Carcinoma, metastatic, uterus																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver			X											X												3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X			X							X			6
Adenoma, multiple									X																X	2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, mesentery																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant							X		X			X			X		X	X	X	X			X	X		17

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	2 7 9	4 3 0	5 9 3	5 9 6	6 2 9	6 3 6	6 5 9	6 7 1	6 7 6	6 8 2	6 8 2	6 8 8	7 0 2	7 1 5	7 1 7	7 1 9	7 2 1	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 8 4	3 5 5	3 5 9	3 9 7	3 6 9	3 8 9	3 5 3	3 6 5	3 9 6	3 6 0	3 7 0	3 9 0	3 5 6	3 7 6	3 7 2	3 8 2	3 5 8	3 9 8	3 7 1	3 7 3	3 7 4	3 7 5	3 7 7	3 7 8	3 7 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Intestine large, cecum	A	+	+	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	A	A	+	+	+	+	M	+	A	A	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	A	+	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, tissue NOS										X															
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma, multiple																									
Hepatocellular carcinoma								X																	
Hepatocellular carcinoma, multiple																							X		
Hepatocellular adenoma											X	X				X		X							
Hepatocellular adenoma, multiple						X				X	X			X					X		X	X	X	X	
Histiocytic sarcoma				X																					
Ito cell tumor malignant											X														
Mesentery			+		+	+						+			+		+		+				+		
Hemangiosarcoma					X																				
Pancreas	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Acinus, carcinoma															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS									+	+															
Fibrosarcoma										X															
Schwannoma malignant									X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	737	737	737	
Carcass ID Number	380	351	352	354	361	362	363	364	391	392	393	394	395	357	359	381	383	385	386	387	388	400	366	367	368	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma																	X									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, metastatic, tissue NOS																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma, multiple									X																	1
Hepatocellular carcinoma		X								X							X				X					5
Hepatocellular carcinoma, multiple														X		X										3
Hepatocellular adenoma				X		X						X						X				X				9
Hepatocellular adenoma, multiple	X	X	X		X		X	X	X	X	X			X	X		X		X		X		X	X	X	26
Histiocytic sarcoma																										1
Ito cell tumor malignant																										1
Mesentery	+		+	+			+	+	+	+	+	+		+		+										19
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Acinus, carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma		X														X										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
Tissue NOS																										2
Fibrosarcoma																										1
Schwannoma malignant																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	279	430	593	596	629	636	659	671	676	682	682	688	702	715	717	719	721	722	729	729	729	729	729	729	729
Carcass ID Number	38 4	35 5	39 9	39 7	36 9	38 9	35 3	36 5	39 6	36 0	37 0	39 0	35 6	37 6	37 6	38 2	35 8	39 8	37 1	37 3	37 4	37 5	37 7	37 8	37 9
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Sarcoma stromal																		X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+								+				+		+								
Iliac, osteosarcoma, metastatic, bone			X																						
Mediastinal, sarcoma, metastatic, skin											X														
Pancreatic, carcinoma, metastatic, pancreas															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma							X																		
Subcutaneous tissue, fibrosarcoma																X									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, neurofibroma																									
Subcutaneous tissue, osteosarcoma, metastatic, bone			X																						
Subcutaneous tissue, sarcoma											X			X				X							
Subcutaneous tissue, schwannoma malignant																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma			X																						
Skeletal muscle					+																				
Hemangiosarcoma					X																				
Rhabdomyosarcoma																									
Sarcoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	
Carcass ID Number	38 0	35 1	35 2	35 4	36 1	36 2	36 3	36 4	39 1	39 2	39 3	39 4	39 5	35 7	35 9	38 1	38 3	38 5	38 6	38 7	38 8	40 0	36 6	36 7	36 8				Total Tissues/ Tumors
Genital System																													
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				49
Histiocytic sarcoma																													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Leiomyoma																				X									1
Sarcoma stromal																													1
Hematopoietic System																													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Lymph node		+									+						+								+				8
Iliac, osteosarcoma, metastatic, bone																													1
Mediastinal, sarcoma, metastatic, skin																													1
Pancreatic, carcinoma, metastatic, pancreas																													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Histiocytic sarcoma																													1
Lymph node, mesenteric	I	+	+	+	+	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+	+	+	M	+	+				45
Histiocytic sarcoma																													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				48
Histiocytic sarcoma																													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				48
Histiocytic sarcoma																													1
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Basal cell carcinoma																													1
Subcutaneous tissue, fibrosarcoma					X																								2
Subcutaneous tissue, hemangioma		X																											1
Subcutaneous tissue, neurofibroma														X															1
Subcutaneous tissue, osteosarcoma, metastatic, bone																													1
Subcutaneous tissue, sarcoma																												X	4
Subcutaneous tissue, schwannoma malignant																													1
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				50
Osteosarcoma																													1
Skeletal muscle			+													+						+			+				5
Hemangiosarcoma																													1
Rhabdomyosarcoma			X																										1
Sarcoma																X												X	2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	279	430	593	596	629	636	659	671	676	682	682	688	702	715	717	719	721	721	729	729	729	729	729	729
Carcass ID Number	38**4**	35**5**	39**9**	39**7**	36**9**	38**9**	35**3**	36**5**	39**6**	36**0**	37**0**	39**0**	35**6**	37**6**	37**2**	38**2**	35**8**	39**8**	37**1**	37**3**	37**4**	37**5**	37**7**	37**9**
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve													+											
Spinal cord													+											
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X									X					X		X		
Alveolar/bronchiolar carcinoma																							X	
Fibrosarcoma, metastatic, skin																X								
Hepatocellular carcinoma, metastatic, liver																								
Osteosarcoma, metastatic, bone			X																					
Sarcoma, metastatic, skin														X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X	X				X							
Carcinoma							X																	
Urinary System																								
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, tissue NOS										X														
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																				
Lymphoma malignant		X									X						X			X			X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid: 1,000 mg/L

Number of Days on Study	729	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	737	737	737	
Carcass ID Number	38040	35051	35052	35054	36061	36062	36063	36064	36091	39902	39903	39904	39905	39905	35907	38101	38103	38105	38106	38107	38108	40006	36066	36067	36068	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X								X							6
Alveolar/bronchiolar carcinoma											X															2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver										X		X				X	X									4
Osteosarcoma, metastatic, bone																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X						X							X			X								X	8
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, tissue NOS																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant	X	X	X							X	X			X	X		X	X								14

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Harderian Gland: Adenoma				
Overall rate[a]	9/50 (18%)	4/50 (8%)	8/50 (16%)	8/50 (16%)
Adjusted rate[b]	19.3%	8.6%	17.8%	17.6%
Terminal rate[c]	6/38 (16%)	2/35 (6%)	5/32 (16%)	5/32 (16%)
First incidence (days)	591	487	622	688
Poly-3 test[d]	P=0.334	P=0.116N	P=0.532N	P=0.525N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	10/50 (20%)	5/50 (10%)	10/50 (20%)	9/50 (18%)
Adjusted rate	21.4%	10.7%	22.1%	19.7%
Terminal rate	7/38 (18%)	2/35 (6%)	6/32 (19%)	5/32 (16%)
First incidence (days)	591	487	622	659
Poly-3 test	P=0.324	P=0.129N	P=0.568	P=0.521N
Liver: Hepatocellular Adenoma				
Overall rate	19/49 (39%)	26/50 (52%)	32/50 (64%)	35/49 (71%)
Adjusted rate	41.4%	56.8%	69.7%	75.9%
Terminal rate	18/38 (47%)	22/35 (63%)	26/32 (81%)	28/32 (88%)
First incidence (days)	653	694	573	636
Poly-3 test	P<0.001	P=0.098	P=0.004	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	12/50 (24%)	8/49 (16%)
Adjusted rate	6.5%	6.6%	26.7%	17.7%
Terminal rate	1/38 (3%)	2/35 (6%)	9/32 (28%)	7/32 (22%)
First incidence (days)	658	694	617	671
Poly-3 test	P=0.019	P=0.659	P=0.009	P=0.094
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	22/49 (45%)[e]	28/50 (56%)	37/50 (74%)[e]	37/49 (76%)
Adjusted rate	47.6%	61.2%	79.5%	79.8%
Terminal rate	19/38 (50%)	24/35 (69%)	28/32 (88%)	29/32 (91%)
First incidence (days)	653	694	573	636
Poly-3 test	P<0.001	P=0.131	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	4/49 (8%)	3/50 (6%)	13/50 (26%)	9/49 (18%)
Adjusted rate	8.7%	6.6%	28.8%	19.9%
Terminal rate	2/38 (5%)	2/35 (6%)	9/32 (28%)	8/32 (25%)
First incidence (days)	658	694	617	671
Poly-3 test	P=0.015	P=0.504N	P=0.012	P=0.109
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rate	2.2%	6.5%	6.7%	13.2%
Terminal rate	1/38 (3%)	2/35 (6%)	1/32 (3%)	4/32 (13%)
First incidence (days)	729 (T)	490	553	636
Poly-3 test	P=0.044	P=0.307	P=0.297	P=0.054
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	4.4%	10.8%	11.0%	15.4%
Terminal rate	2/38 (5%)	3/35 (9%)	2/32 (6%)	5/32 (16%)
First incidence (days)	729 (T)	490	553	636
Poly-3 test	P=0.095	P=0.219	P=0.210	P=0.076

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	1/49 (2%)	0/49 (0%)	3/49 (6%)	2/46 (4%)
Adjusted rate	2.2%	0.0%	6.7%	4.7%
Terminal rate	1/38 (3%)	0/35 (0%)	1/32 (3%)	2/32 (6%)
First incidence (days)	729 (T)	—[f]	553	729 (T)
Poly-3 test	P=0.158	P=0.503N	P=0.300	P=0.478
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	2/47 (4%)	4/49 (8%)	0/49 (0%)	1/49 (2%)
Adjusted rate	4.6%	9.0%	0.0%	2.3%
Terminal rate	1/36 (3%)	3/34 (9%)	0/31 (0%)	1/31 (3%)
First incidence (days)	720	694	—	729 (T)
Poly-3 test	P=0.114N	P=0.347	P=0.239N	P=0.496N
Skin (Subcutaneous Tissue): Fibrous Histiocytoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.5%	0.0%	0.0%	0.0%
Terminal rate	3/38 (8%)	0/35 (0%)	0/32 (0%)	0/32 (0%)
First incidence (days)	729 (T)	—	—	—
Poly-3 test	P=0.092N	P=0.121N	P=0.125N	P=0.122N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted rate	2.2%	2.2%	2.2%	8.8%
Terminal rate	1/38 (3%)	0/35 (0%)	0/32 (0%)	1/32 (3%)
First incidence (days)	729 (T)	710	659	682
Poly-3 test	P=0.063	P=0.759	P=0.754	P=0.175
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted rate	8.7%	6.5%	6.7%	13.2%
Terminal rate	3/38 (8%)	0/35 (0%)	1/32 (3%)	2/32 (6%)
First incidence (days)	710	490	573	682
Poly-3 test	P=0.210	P=0.497N	P=0.511N	P=0.361
Stomach (Forestomach): Squamous Cell Papilloma or Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.2%	2.2%	6.8%	2.2%
Terminal rate	1/38 (3%)	1/35 (3%)	2/32 (6%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	718	729 (T)
Poly-3 test	P=0.503	P=0.758	P=0.293	P=0.757
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.5%	0.0%	0.0%	0.0%
Terminal rate	2/38 (5%)	0/35 (0%)	0/32 (0%)	0/32 (0%)
First incidence (days)	714	—	—	—
Poly-3 test	P=0.091N	P=0.121N	P=0.126N	P=0.122N
All Organs: Hemangioma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.5%	2.2%	4.5%	2.2%
Terminal rate	3/38 (8%)	1/35 (3%)	1/32 (3%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	659	729 (T)
Poly-3 test	P=0.353N	P=0.309N	P=0.514N	P=0.312N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	8.7%	6.6%	8.9%	4.4%
Terminal rate	3/38 (8%)	3/35 (9%)	1/32 (3%)	1/32 (3%)
First incidence (days)	653	729 (T)	617	629
Poly-3 test	P=0.331N	P=0.509N	P=0.629	P=0.345N
All Organs: Malignant Lymphoma				
Overall rate	27/50 (54%)	24/50 (48%)	17/50 (34%)	14/50 (28%)
Adjusted rate	57.8%	51.7%	37.5%	30.3%
Terminal rate	25/38 (66%)	21/35 (60%)	12/32 (38%)	11/32 (34%)
First incidence (days)	474	490	618	430
Poly-3 test	P=0.002N	P=0.348N	P=0.036N	P=0.005N
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	33/50 (66%)	41/50 (82%)	38/50 (76%)
Adjusted rate	60.9%	69.0%	85.5%	82.2%
Terminal rate	23/38 (61%)	25/35 (71%)	28/32 (88%)	30/32 (94%)
First incidence (days)	563	487	553	636
Poly-3 test	P=0.005	P=0.267	P=0.004	P=0.015
All Organs: Malignant Neoplasms				
Overall rate	36/50 (72%)	37/50 (74%)	34/50 (68%)	32/50 (64%)
Adjusted rate	74.6%	76.9%	70.8%	66.0%
Terminal rate	29/38 (76%)	27/35 (77%)	19/32 (59%)	18/32 (56%)
First incidence (days)	474	383	573	430
Poly-3 test	P=0.124N	P=0.491	P=0.421N	P=0.240N
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	43/50 (86%)	46/50 (92%)	48/50 (96%)
Adjusted rate	85.1%	88.0%	94.6%	97.9%
Terminal rate	31/38 (82%)	31/35 (89%)	30/32 (94%)	31/32 (97%)
First incidence (days)	474	383	553	430
Poly-3 test	P=0.008	P=0.452	P=0.103	P=0.025

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pancreatic islets, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] One hepatoblastoma occurred in an animal that also had a hepatocellular adenoma
[f] Not applicable; no neoplasms in animal group

TABLE D4a
Historical Incidence of Hepatocellular Neoplasms in Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Drinking Water Studies			
Bromodichloromethane	24/50	13/50	30/50
Dibromoacetic acid	19/49	3/49	22/49
Dipropylene glycol	11/50	7/50	17/50
Sodium chlorate	30/49	3/49	31/49
Sodium nitrite	9/50	2/50	10/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	93/248 (37.5%)	28/248 (11.3%)	110/248 (44.4%)
Mean ± standard deviation	37.6% ± 18.0%	11.3% ± 9.1%	44.4% ± 18.1%
Range	18%-61%	4%-26%	20%-63%
Overall Historical Incidence			
Total (%)	312/1,549 (20.1%)	128/1,549 (8.3%)	408/1,549 (26.3%)
Mean ± standard deviation	21.2% ± 13.4%	8.7% ± 5.8%	27.7% ± 15.5%
Range	6%-61%	0%-26%	8%-63%

[a] Data as of January 26, 2005

TABLE D4b
Historical Incidence of Alveolar/bronchiolar Neoplasms in Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Drinking Water Studies			
Bromodichloromethane	6/50	1/50	6/50
Dibromoacetic acid	1/50	1/50	2/50
Dipropylene glycol	2/50	2/50	3/50
Sodium chlorate	3/50	1/50	4/50
Sodium nitrite	1/50	0/50	1/50
Overall Historical Incidence: Drinking Water Studies			
Total (%)	13/250 (5.2%)	5/250 (2.0%)	16/250 (6.4%)
Mean ± standard deviation	5.2% ± 4.2%	2.0% ± 1.4%	6.4% ± 3.9%
Range	2%-12%	0%-4%	2%-12%
Overall Historical Incidence			
Total (%)	80/1,552 (5.2%)	40/1,552 (2.6%)	117/1,552 (7.5%)
Mean ± standard deviation	5.1% ± 3.5%	2.5% ± 2.6%	7.4% ± 3.8%
Range	0%-12%	0%-12%	0%-14%

[a] Data as of January 26, 2005

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Disposition Summary								
Animals initially in study	50		50		50		50	
Early deaths								
Moribund	2		2		5		7	
Natural deaths	10		13		13		11	
Survivors								
Died last week of study					1			
Terminal sacrifice	38		35		31		32	
Animals examined microscopically	50		50		50		50	
Alimentary System								
Intestine large, rectum	(49)		(49)		(48)		(49)	
Ulcer					1	(2%)		
Intestine large, cecum	(47)		(46)		(49)		(46)	
Edema	2	(4%)	1	(2%)			3	(7%)
Inflammation, chronic			1	(2%)			1	(2%)
Epithelium, hyperplasia					1	(2%)		
Intestine small, duodenum	(46)		(48)		(48)		(45)	
Epithelium, hyperplasia			1	(2%)				
Intestine small, jejunum	(46)		(47)		(49)		(43)	
Hyperplasia, lymphoid			2	(4%)			2	(5%)
Intestine small, ileum	(45)		(47)		(47)		(46)	
Inflammation, chronic			1	(2%)				
Liver	(49)		(50)		(50)		(49)	
Angiectasis	1	(2%)	2	(4%)				
Basophilic focus			1	(2%)	3	(6%)	3	(6%)
Clear cell focus	3	(6%)	1	(2%)	8	(16%)	5	(10%)
Eosinophilic focus	7	(14%)	6	(12%)	10	(20%)	9	(18%)
Hematopoietic cell proliferation	2	(4%)	4	(8%)	2	(4%)	2	(4%)
Hepatodiaphragmatic nodule							2	(4%)
Hyperplasia, lymphoid	2	(4%)	1	(2%)				
Infarct							1	(2%)
Infiltration cellular, mixed cell	7	(14%)	7	(14%)	4	(8%)	9	(18%)
Inflammation, chronic active					1	(2%)		
Mixed cell focus	2	(4%)	6	(12%)	3	(6%)	1	(2%)
Necrosis, focal	3	(6%)	2	(4%)	3	(6%)	2	(4%)
Tension lipidosis	1	(2%)	3	(6%)				
Centrilobular, necrosis			1	(2%)	4	(8%)	4	(8%)
Hepatocyte, vacuolization cytoplasmic	2	(4%)	7	(14%)	4	(8%)	2	(4%)
Kupffer cell, pigmentation	3	(6%)					3	(6%)
Mesentery	(28)		(20)		(16)		(19)	
Fat, necrosis	22	(79%)	18	(90%)	11	(69%)	13	(68%)
Pancreas	(49)		(49)		(49)		(47)	
Atrophy			1	(2%)	1	(2%)	3	(6%)
Cyst					1	(2%)	3	(6%)
Inflammation, chronic							1	(2%)
Acinus, cytoplasmic alteration	1	(2%)						
Salivary glands	(50)		(49)		(50)		(50)	
Hyperplasia, lymphoid	15	(30%)	13	(27%)	16	(32%)	10	(20%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Alimentary System (continued)								
Stomach, forestomach	(49)		(50)		(50)		(49)	
Erosion			1	(2%)				
Inflammation, chronic	1	(2%)	2	(4%)	2	(4%)	1	(2%)
Ulcer	1	(2%)	1	(2%)	1	(2%)	3	(6%)
Epithelium, hyperplasia	4	(8%)	5	(10%)			4	(8%)
Stomach, glandular	(49)		(50)		(50)		(49)	
Erosion			1	(2%)			1	(2%)
Pylorus, epithelium, hyperplasia, atypical			1	(2%)				
Tooth					(1)			
Malformation					1	(100%)		
Cardiovascular System								
Blood vessel	(1)		(1)		(1)			
Hypertrophy					1	(100%)		
Inflammation, chronic active					1	(100%)		
Heart	(50)		(49)		(50)		(50)	
Cardiomyopathy					1	(2%)	1	(2%)
Inflammation, chronic			1	(2%)			1	(2%)
Inflammation, chronic active							1	(2%)
Mineralization			1	(2%)	1	(2%)	2	(4%)
Endocrine System								
Adrenal cortex	(50)		(50)		(50)		(49)	
Accessory adrenal cortical nodule	9	(18%)	11	(22%)	6	(12%)	9	(18%)
Hyperplasia, focal			2	(4%)			1	(2%)
Hypertrophy, focal			1	(2%)				
Capsule, hyperplasia			1	(2%)			1	(2%)
Adrenal medulla	(50)		(50)		(50)		(49)	
Hyperplasia			2	(4%)	1	(2%)	1	(2%)
Islets, pancreatic	(49)		(49)		(49)		(46)	
Hyperplasia	2	(4%)	5	(10%)	3	(6%)	3	(7%)
Parathyroid gland	(45)		(49)		(47)		(49)	
Cyst	2	(4%)	1	(2%)	1	(2%)	3	(6%)
Pituitary gland	(47)		(49)		(49)		(49)	
Pars distalis, angiectasis	2	(4%)	3	(6%)	1	(2%)	1	(2%)
Pars distalis, cyst	2	(4%)	2	(4%)	1	(2%)	1	(2%)
Pars distalis, hyperplasia, focal	4	(9%)	9	(18%)	4	(8%)	7	(14%)
Pars intermedia, hyperplasia, focal	1	(2%)						
Thyroid gland	(50)		(50)		(50)		(50)	
Degeneration, cystic	10	(20%)	26	(52%)	16	(32%)	14	(28%)
Follicular cell, hyperplasia	8	(16%)	1	(2%)	1	(2%)	2	(4%)
General Body System								
None								

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Genital System								
Clitoral gland	(50)		(48)		(48)		(49)	
Cyst			1	(2%)				
Ovary	(49)		(47)		(47)		(49)	
Angiectasis	5	(10%)	3	(6%)	9	(19%)	7	(14%)
Cyst	14	(29%)	12	(26%)	14	(30%)	22	(45%)
Corpus luteum, hyperplasia	1	(2%)	1	(2%)				
Granulosa cell, hyperplasia	1	(2%)						
Interstitial cell, hyperplasia							1	(2%)
Uterus	(50)		(50)		(50)		(50)	
Angiectasis			4	(8%)	1	(2%)	2	(4%)
Hyperplasia, cystic	44	(88%)	42	(84%)	44	(88%)	39	(78%)
Inflammation, chronic	1	(2%)	1	(2%)	1	(2%)		
Metaplasia, squamous	1	(2%)			1	(2%)	1	(2%)
Hematopoietic System								
Bone marrow	(50)		(50)		(50)		(50)	
Hyperplasia	20	(40%)	26	(52%)	24	(48%)	20	(40%)
Infiltration cellular, mast cell			1	(2%)				
Lymph node	(12)		(13)		(11)		(8)	
Hyperplasia, lymphoid			1	(8%)				
Bronchial, hemorrhage			1	(8%)				
Bronchial, hyperplasia, lymphoid			1	(8%)				
Deep cervical, hemorrhage							1	(13%)
Iliac, hematopoietic cell proliferation			1	(8%)				
Iliac, hemorrhage	1	(8%)					1	(13%)
Iliac, hyperplasia, lymphoid	1	(8%)	1	(8%)	1	(9%)	2	(25%)
Iliac, pigmentation	1	(8%)						
Inguinal, hematopoietic cell proliferation			1	(8%)				
Inguinal, hyperplasia, lymphoid			2	(15%)				
Mediastinal, hemorrhage	1	(8%)						
Mediastinal, hyperplasia, lymphoid	1	(8%)	1	(8%)	1	(9%)	1	(13%)
Mediastinal, pigmentation	1	(8%)						
Pancreatic, hyperplasia, lymphoid					1	(9%)		
Renal, hyperplasia, lymphoid	1	(8%)			1	(9%)	1	(13%)
Lymph node, mandibular	(48)		(49)		(47)		(50)	
Atrophy			1	(2%)	1	(2%)	1	(2%)
Hematopoietic cell proliferation	1	(2%)	1	(2%)			2	(4%)
Hemorrhage			2	(4%)	2	(4%)	1	(2%)
Hyperplasia, lymphoid	13	(27%)	6	(12%)	8	(17%)	9	(18%)
Pigmentation	18	(38%)	25	(51%)	17	(36%)	23	(46%)
Lymph node, mesenteric	(49)		(49)		(48)		(45)	
Angiectasis					1	(2%)		
Atrophy					2	(4%)	1	(2%)
Ectasia					1	(2%)		
Hematopoietic cell proliferation	2	(4%)			2	(4%)	1	(2%)
Hemorrhage	1	(2%)	1	(2%)	1	(2%)	5	(11%)
Hyperplasia, lymphoid	8	(16%)	9	(18%)	7	(15%)	5	(11%)
Pigmentation					1	(2%)	1	(2%)
Spleen	(50)		(50)		(50)		(48)	
Hematopoietic cell proliferation	34	(68%)	42	(84%)	35	(70%)	34	(71%)
Necrosis	1	(2%)						
Pigmentation	5	(10%)	5	(10%)	1	(2%)	2	(4%)
Lymphoid follicle, atrophy			1	(2%)	2	(4%)	2	(4%)
Lymphoid follicle, hyperplasia	8	(16%)	11	(22%)	14	(28%)	12	(25%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L		500 mg/L		1,000 mg/L	
Hematopoietic System (continued)								
Thymus	(44)		(47)		(47)		(48)	
Atrophy	8	(18%)	9	(19%)	11	(23%)	13	(27%)
Hemorrhage	1	(2%)						
Hyperplasia, lymphoid			3	(6%)	3	(6%)	2	(4%)
Integumentary System								
Mammary gland	(50)		(50)		(50)		(50)	
Hyperplasia	5	(10%)	6	(12%)	2	(4%)	5	(10%)
Skin	(50)		(50)		(50)		(50)	
Edema			1	(2%)	1	(2%)	1	(2%)
Erosion					1	(2%)		
Ulcer	2	(4%)	1	(2%)	1	(2%)	1	(2%)
Epidermis, hyperplasia	2	(4%)	1	(2%)	2	(4%)	1	(2%)
Musculoskeletal System								
Bone	(50)		(50)		(50)		(50)	
Myelofibrosis	1	(2%)	2	(4%)	1	(2%)	2	(4%)
Skeletal muscle	(3)		(4)		(2)		(5)	
Inflammation, chronic active							1	(20%)
Nervous System								
Brain	(50)		(49)		(50)		(50)	
Compression	1	(2%)	1	(2%)	1	(2%)		
Hemorrhage			2	(4%)				
Necrosis			1	(2%)	1	(2%)		
Peripheral nerve			(1)		(1)		(1)	
Atrophy							1	(100%)
Spinal cord			(1)		(1)		(1)	
Necrosis			1	(100%)				
Respiratory System								
Lung	(50)		(50)		(50)		(50)	
Congestion					2	(4%)		
Hemorrhage			2	(4%)	2	(4%)	3	(6%)
Hyperplasia, lymphoid	5	(10%)	5	(10%)	1	(2%)	3	(6%)
Infiltration cellular, histiocyte	1	(2%)	2	(4%)	2	(4%)	4	(8%)
Alveolar epithelium, hyperplasia	3	(6%)	3	(6%)			4	(8%)
Perivascular, inflammation, chronic active							1	(2%)
Nose	(50)		(50)		(50)		(50)	
Inflammation, chronic							1	(2%)
Special Senses System								
Eye	(50)		(50)		(50)		(50)	
Atrophy					1	(2%)		
Cataract					2	(4%)	2	(4%)
Inflammation, chronic	2	(4%)	2	(4%)	3	(6%)	3	(6%)
Cornea, hyperplasia	1	(2%)			4	(8%)		
Cornea, mineralization							1	(2%)
Harderian gland	(49)		(50)		(50)		(50)	
Hyperplasia, focal	2	(4%)	4	(8%)	4	(8%)	2	(4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L	50 mg/L	500 mg/L	1,000 mg/L
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Cyst		1 (2%)		1 (2%)
Hydronephrosis			1 (2%)	1 (2%)
Hyperplasia, lymphoid	7 (14%)	2 (4%)	5 (10%)	8 (16%)
Infarct	3 (6%)	8 (16%)	6 (12%)	8 (16%)
Nephropathy	14 (29%)	8 (16%)	15 (30%)	12 (24%)
Renal tubule, accumulation, hyaline droplet	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Renal tubule, dilatation		2 (4%)	1 (2%)	1 (2%)
Renal tubule, necrosis		1 (2%)		1 (2%)
Renal tubule, pigmentation	1 (2%)		3 (6%)	1 (2%)
Urinary bladder	(50)	(49)	(50)	(49)
Edema	2 (4%)			
Hyperplasia, lymphoid	3 (6%)	5 (10%)	3 (6%)	2 (4%)
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Dibromoacetic acid was sent to the laboratory as a coded aliquot from Research Triangle Institute (Research Triangle Park, NC). It was incubated with the *Salmonella typhimurium* tester strains TA98 and TA100 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37º C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37º C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of dibromoacetic acid. In the absence of toxicity, 10,000 µg/plate was selected as the high dose. All positive trials were repeated under the conditions that elicited the positive response.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive, although positive calls are typically reserved for increases in mutant colonies that are at least two-fold over background.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the termination of the 3-month toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of up to 10 animals per exposure group. In addition, the percentage of polychromatic erythrocytes (PCEs) in a population of 1,000 erythrocytes was determined as a measure of bone marrow toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results from 3-month studies were accepted without repeat tests because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Dibromoacetic acid, tested over a concentration range of 33 to 10,000 µg/plate, was mutagenic in *S. typhimurium* strain TA100 with and without 30% rat or hamster liver metabolic activation enzymes (S9); no activity was detected in strain TA98, with or without rat or hamster liver S9 enzymes (Table E1). Increased frequencies of micronucleated NCEs were observed in peripheral blood samples from male B6C3F_1 mice administered 125 to 2,000 mg dibromoacetic acid/L in drinking water for 3 months; no increases in NCEs were seen in female mice similarly exposed (Table E2). No evidence of bone marrow toxicity, as measured by the percentage of immature (polychromatic) erythrocytes among total erythrocytes, was observed in either male or female mice.

TABLE E1
Mutagenicity of Dibromoacetic Acid in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] -S9 Trial 1	-S9 Trial 2	+ 30% hamster S9 Trial 1	+ 30% hamster S9 Trial 2	+30% rat S9 Trial 1	+30% rat S9 Trial 2
TA100	0	148 ± 5.0	108 ± 5.9	144 ± 9.5	125 ± 6.8	165 ± 2.8	149 ± 7.0
	33	140 ± 8.8	126 ± 3.4		141 ± 9.8		164 ± 9.1
	100	167 ± 4.9	154 ± 7.4	212 ± 6.1	180 ± 4.2	253 ± 9.5	289 ± 10.5
	333	261 ± 11.5	196 ± 4.5	339 ± 14.5	334 ± 27.1	356 ± 6.6	351 ± 19.3
	1,000	469 ± 14.5	360 ± 21.4	459 ± 16.4	388 ± 15.3	445 ± 20.9	434 ± 26.6
	3,333	981 ± 20.3	770 ± 23.3	1,041 ± 63.5	754 ± 17.7	930 ± 28.1	802 ± 24.1
	10,000			1,361 ± 37.3		1,294 ± 29.4	
Trial Summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control[c]		1,187 ± 15.9	1,352 ± 27.4	1,250 ± 62.8	763 ± 25.2	838 ± 37.4	673 ± 38.4
TA98	0	22 ± 1.8		23 ± 3.2		20 ± 2.1	
	33	22 ± 1.7					
	100	18 ± 1.8		18 ± 2.0		22 ± 3.2	
	333	22 ± 3.3		22 ± 3.8		16 ± 2.9	
	1,000	19 ± 3.5		19 ± 1.2		25 ± 0.6	
	3,333	23 ± 4.5		21 ± 1.7		18 ± 2.1	
	10,000			23 ± 1.5		17 ± 1.2	
Trial Summary		Negative		Negative		Negative	
Positive control		422 ± 9.0		904 ± 33.8		513 ± 31.9	

[a] Study was performed at SRI International. The detailed protocol is presented by Zeiger *et al.* (1992). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100) and 4-nitro-*o*-phenlyenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Administration of Dibromoacetic Acid in Drinking Water for 3 Months[a]

Compound	Exposure Concentration (mg/L)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P-Value[c]	PCEs[b] (%)
Male					
Tap water	0	10	1.80 ± 0.33		3.0 ± 0.2
Dibromoacetic acid	125	10	2.30 ± 0.47	0.2172	2.8 ± 0.1
	250	10	3.30 ± 0.56	0.0177	2.8 ± 0.1
	500	10	3.20 ± 0.42	0.0237	2.7 ± 0.1
	1,000	9	4.00 ± 0.50	0.0022	2.8 ± 0.2
	2,000	10	3.60 ± 0.56	0.0071	3.0 ± 0.1
			P=0.010[d]		
Female					
Tap water	0	10	2.30 ± 0.56		2.8 ± 0.1
Dibromoacetic acid	125	10	2.10 ± 0.43	0.6186	2.4 ± 0.1
	250	10	1.70 ± 0.30	0.8289	2.6 ± 0.1
	500	10	2.10 ± 0.28	0.6186	2.8 ± 0.1
	1,000	10	2.20 ± 0.44	0.5593	2.7 ± 0.1
	2,000	10	2.20 ± 0.29	0.5593	2.7 ± 0.1
			P=0.397		

[a] Study was performed at ILS, Inc. The detailed protocol presented by MacGregor *et al.* (1990). PCE=polychromatic erythrocyte; NCE=normochromatic erythrocyte.
[b] Mean ± standard error
[c] Pairwise comparison with the untreated control group; significant at $P \leq 0.005$ (ILS, 1990)
[d] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at $P \leq 0.025$ (ILS, 1990)

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male						
Hematology						
Day 4	10	10	10	10	10	10
Day 21	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Hematocrit (%)						
Day 4	45.3 ± 0.8	42.5 ± 0.9	44.2 ± 0.7	43.7 ± 0.5	45.1 ± 0.9	45.7 ± 0.6
Day 21	46.2 ± 0.7	45.5 ± 0.6	45.6 ± 0.6	45.3 ± 0.5	45.5 ± 0.6	42.8 ± 0.6**
Week 14	46.8 ± 0.3	45.7 ± 0.5	45.4 ± 0.6	45.3 ± 0.5*	45.5 ± 0.3	45.3 ± 0.3
Hemoglobin (g/dL)						
Day 4	14.7 ± 0.3	13.9 ± 0.3	14.5 ± 0.2	14.3 ± 0.2	14.7 ± 0.3	15.1 ± 0.2
Day 21	15.4 ± 0.2	15.0 ± 0.2	15.2 ± 0.2	15.0 ± 0.2	15.0 ± 0.2	14.2 ± 0.2**
Week 14	15.4 ± 0.1	15.1 ± 0.2	15.0 ± 0.1*	15.1 ± 0.1	15.1 ± 0.1	15.0 ± 0.1
Erythrocytes (10^6/µL)						
Day 4	7.30 ± 0.12	6.90 ± 0.15	7.20 ± 0.11	7.11 ± 0.11	7.49 ± 0.16	7.66 ± 0.12
Day 21	7.65 ± 0.13	7.49 ± 0.11	7.49 ± 0.10	7.42 ± 0.06	7.63 ± 0.10	7.26 ± 0.11
Week 14	9.08 ± 0.08	8.86 ± 0.10	8.78 ± 0.11	8.80 ± 0.09	8.85 ± 0.07	8.89 ± 0.06
Reticulocytes (10^6/µL)						
Day 4	8.28 ± 0.32	8.08 ± 0.23	8.38 ± 0.27	7.99 ± 0.30	7.35 ± 0.30*	5.86 ± 0.23**
Day 21	4.79 ± 0.10	5.10 ± 0.10	5.05 ± 0.13	5.04 ± 0.17	4.69 ± 0.13	4.52 ± 0.16
Week 14	2.53 ± 0.08	2.86 ± 0.09*	2.69 ± 0.06	2.76 ± 0.05	2.64 ± 0.07	2.68 ± 0.04
Mean cell volume (fL)						
Day 4	62.0 ± 0.3	61.6 ± 0.3	61.5 ± 0.4	61.4 ± 0.2	60.3 ± 0.5*	59.7 ± 0.2**
Day 21	60.5 ± 0.3	60.8 ± 0.5	60.9 ± 0.4	61.1 ± 0.4	59.7 ± 0.3	59.0 ± 0.3*
Week 14	51.6 ± 0.2	51.5 ± 0.2	51.7 ± 0.1	51.5 ± 0.2	51.5 ± 0.2	50.9 ± 0.2
Mean cell hemoglobin (pg)						
Day 4	20.1 ± 0.1	20.1 ± 0.1	20.1 ± 0.1	20.0 ± 0.1	19.7 ± 0.2	19.8 ± 0.1*
Day 21	20.1 ± 0.1	20.1 ± 0.2	20.4 ± 0.1	20.3 ± 0.1	19.7 ± 0.1*	19.6 ± 0.1**
Week 14	17.0 ± 0.1	17.0 ± 0.1	17.1 ± 0.1	17.2 ± 0.1	17.0 ± 0.1	16.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 4	32.5 ± 0.2	32.7 ± 0.1	32.7 ± 0.2	32.7 ± 0.2	32.7 ± 0.2	33.1 ± 0.2
Day 21	33.3 ± 0.2	33.1 ± 0.2	33.4 ± 0.1	33.2 ± 0.2	33.0 ± 0.1	33.2 ± 0.2
Week 14	33.0 ± 0.2	33.0 ± 0.2	33.0 ± 0.2	33.4 ± 0.2	33.1 ± 0.2	33.2 ± 0.2
Platelets (10^3/µL)						
Day 4	875.8 ± 15.7	920.8 ± 25.7	909.1 ± 13.9	939.0 ± 26.3	868.7 ± 18.5	828.5 ± 24.5
Day 21	869.2 ± 18.6	883.7 ± 13.5	859.6 ± 17.0	894.3 ± 19.7	836.8 ± 9.9	742.2 ± 14.8**
Week 14	636.1 ± 9.9	629.0 ± 14.2	634.7 ± 12.6	646.5 ± 8.9	610.8 ± 8.5	572.2 ± 12.3**
Leukocytes (10^3/µL)						
Day 4	8.09 ± 0.41	8.06 ± 0.43	8.23 ± 0.29	8.53 ± 0.33	8.35 ± 0.36	8.68 ± 0.70
Day 21	9.48 ± 0.39	9.79 ± 0.41	9.55 ± 0.30	9.35 ± 0.50	9.11 ± 0.30	9.36 ± 0.25
Week 14	10.66 ± 0.44	10.20 ± 0.45	10.39 ± 0.45	10.39 ± 0.46	9.83 ± 0.23	10.36 ± 0.37
Segmented neutrophils (10^3/µL)						
Day 4	1.13 ± 0.04	1.13 ± 0.05	1.13 ± 0.05	1.15 ± 0.04	1.16 ± 0.08	1.09 ± 0.09
Day 21	0.99 ± 0.03	0.97 ± 0.03	0.85 ± 0.03	0.92 ± 0.04	0.90 ± 0.06	1.02 ± 0.04
Week 14	1.21 ± 0.07	1.26 ± 0.03	1.12 ± 0.05	1.13 ± 0.04	1.15 ± 0.04	1.38 ± 0.09
Lymphocytes (10^3/µL)						
Day 4	6.55 ± 0.36	6.46 ± 0.40	6.65 ± 0.25	6.90 ± 0.31	6.73 ± 0.29	7.06 ± 0.56
Day 21	8.08 ± 0.36	8.36 ± 0.38	8.27 ± 0.26	7.99 ± 0.44	7.76 ± 0.28	7.87 ± 0.19
Week 14	8.46 ± 0.34	8.04 ± 0.39	8.27 ± 0.39	8.18 ± 0.40	7.78 ± 0.18	7.98 ± 0.26
Activated lymphocytes (10^3/µL)						
Day 4	0.26 ± 0.03	0.31 ± 0.03	0.30 ± 0.03	0.33 ± 0.02	0.33 ± 0.02	0.37 ± 0.04**
Day 21	0.27 ± 0.03	0.31 ± 0.03	0.30 ± 0.03	0.29 ± 0.03	0.32 ± 0.02	0.35 ± 0.02
Week 14	0.81 ± 0.05	0.72 ± 0.07	0.81 ± 0.06	0.87 ± 0.05	0.72 ± 0.04	0.85 ± 0.07

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male (continued)						
Hematology (continued)						
Day 4	10	10	10	10	10	10
Day 21	10	10	10	10	10	10
Week 14	10	10	10	10	10	9
Monocytes (10^3/µL)						
Day 4	0.11 ± 0.02	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.10 ± 0.02
Day 21	0.10 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.10 ± 0.02	0.08 ± 0.02
Week 14	0.09 ± 0.01	0.10 ± 0.02	0.11 ± 0.04	0.13 ± 0.03	0.10 ± 0.01	0.07 ± 0.01
Basophils (10^3/µL)						
Day 4	0.013 ± 0.004	0.014 ± 0.003	0.014 ± 0.003	0.014 ± 0.002	0.015 ± 0.004	0.017 ± 0.004
Day 21	0.013 ± 0.002	0.014 ± 0.003	0.014 ± 0.003	0.015 ± 0.003	0.016 ± 0.002	0.016 ± 0.002
Week 14	0.026 ± 0.004	0.017 ± 0.004	0.022 ± 0.004	0.030 ± 0.004	0.022 ± 0.003	0.022 ± 0.004
Eosinophils (10^3/µL)						
Day 4	0.03 ± 0.00	0.03 ± 0.01	0.03 ± 0.00	0.02 ± 0.00	0.03 ± 0.00	0.04 ± 0.01
Day 21	0.02 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.04 ± 0.00*
Week 14	0.07 ± 0.01	0.06 ± 0.00	0.06 ± 0.00	0.06 ± 0.00	0.05 ± 0.01*	0.05 ± 0.00
Clinical Chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	12.5 ± 0.3	11.8 ± 0.5	12.1 ± 0.4	13.0 ± 0.3	13.5 ± 0.2	13.8 ± 0.6
Day 21	11.8 ± 0.3	11.8 ± 0.4	12.8 ± 0.4	11.6 ± 0.2	13.3 ± 0.4**	14.1 ± 0.3**
Week 14	16.9 ± 0.5	12.0 ± 0.5**	14.3 ± 0.9	14.4 ± 0.5	12.3 ± 0.5**	13.1 ± 0.6**
Creatinine (mg/dL)						
Day 4	0.45 ± 0.02	0.42 ± 0.01	0.44 ± 0.02	0.43 ± 0.02	0.42 ± 0.01	0.41 ± 0.01
Day 21	0.55 ± 0.02	0.54 ± 0.02	0.53 ± 0.02	0.52 ± 0.01	0.48 ± 0.01**	0.49 ± 0.01**
Week 14	0.55 ± 0.02	0.55 ± 0.02	0.54 ± 0.02	0.55 ± 0.02	0.55 ± 0.02	0.51 ± 0.01
Total protein (g/dL)						
Day 4	5.5 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.4 ± 0.1	5.2 ± 0.0*	4.9 ± 0.1**
Day 21	6.3 ± 0.1	6.5 ± 0.1	6.6 ± 0.1*	6.5 ± 0.1	6.5 ± 0.1	6.0 ± 0.1
Week 14	6.7 ± 0.0	6.8 ± 0.1	6.9 ± 0.1*	6.9 ± 0.1*	7.0 ± 0.1**	6.9 ± 0.1**
Albumin (g/dL)						
Day 4	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	3.9 ± 0.0	3.8 ± 0.1*
Day 21	4.5 ± 0.0	4.7 ± 0.1	4.7 ± 0.1*	4.7 ± 0.1	4.7 ± 0.1*	4.5 ± 0.1
Week 14	4.8 ± 0.0	4.9 ± 0.1*	5.1 ± 0.1**	5.0 ± 0.1**	5.1 ± 0.0**	5.2 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 4	80 ± 2	77 ± 2	77 ± 3	78 ± 2	87 ± 1*	85 ± 2
Day 21	54 ± 1	52 ± 1	55 ± 3	47 ± 1**	47 ± 1**	47 ± 2**
Week 14	83 ± 4	47 ± 2**	62 ± 7**	52 ± 3**	43 ± 1**	49 ± 2**
Alkaline phosphatase (IU/L)						
Day 4	745 ± 17	754 ± 14	769 ± 25	805 ± 22*	818 ± 17*	788 ± 17*
Day 21	556 ± 8	509 ± 11**	515 ± 16*	516 ± 11*	504 ± 19**	479 ± 7**
Week 14	200 ± 10	182 ± 4	201 ± 10	174 ± 9	186 ± 6	192 ± 6
Creatine kinase (IU/L)						
Day 4	537 ± 31	497 ± 61	472 ± 36	410 ± 26	564 ± 65	426 ± 17
Day 21	306 ± 26	256 ± 20	281 ± 16	318 ± 36	354 ± 52	255 ± 14
Week 14	306 ± 29	207 ± 21	223 ± 28	282 ± 15	219 ± 23	194 ± 17*

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male (continued)						
Clinical Chemistry						
n	10	10	10	10	10	10
Sorbitol dehydrogenase (IU/L)						
Day 4	7 ± 0	8 ± 0	9 ± 0*	9 ± 0**	10 ± 0**	11 ± 0**
Day 21	9 ± 1	9 ± 1	9 ± 1	10 ± 1	11 ± 1	12 ± 1**
Week 14	9 ± 1	8 ± 1	10 ± 1	8 ± 1	9 ± 1	10 ± 1
Bile acids (μmol/L)						
Day 4	34.9 ± 3.1	33.9 ± 2.2	35.9 ± 2.2	38.0 ± 2.7	52.8 ± 3.3**	53.2 ± 2.9**
Day 21	24.9 ± 1.5	26.2 ± 1.2	31.7 ± 1.4**	26.0 ± 0.9	29.0 ± 1.7	24.2 ± 1.1
Week 14	20.4 ± 2.1	16.6 ± 1.7	13.6 ± 0.7*	18.5 ± 1.7	17.8 ± 1.9	16.9 ± 1.5
Female						
Hematology						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	9	9	10
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 4	43.5 ± 0.6	44.5 ± 0.5	45.1 ± 0.7	45.8 ± 1.2	45.5 ± 0.7	46.6 ± 1.0
Day 21	46.2 ± 0.3	45.4 ± 0.4	44.9 ± 0.5	46.8 ± 0.7	44.2 ± 0.4**	43.4 ± 0.8**
Week 14	42.4 ± 0.3	42.9 ± 0.4	42.7 ± 0.3	42.4 ± 0.5	41.5 ± 0.5	40.9 ± 0.5
Hemoglobin (g/dL)						
Day 4	14.3 ± 0.2	14.6 ± 0.2	14.8 ± 0.3	15.2 ± 0.4	15.1 ± 0.3	15.4 ± 0.3
Day 21	15.6 ± 0.1	15.3 ± 0.2	15.3 ± 0.2	15.7 ± 0.2	15.0 ± 0.2*	14.7 ± 0.2**
Week 14	13.7 ± 0.1	13.9 ± 0.1	13.9 ± 0.1	13.8 ± 0.1	13.5 ± 0.2	13.2 ± 0.1*
Erythrocytes (10^6/μL)						
Day 4	7.53 ± 0.11	7.71 ± 0.12	7.76 ± 0.15	7.96 ± 0.19	7.90 ± 0.14	8.23 ± 0.16**
Day 21	7.98 ± 0.07	7.77 ± 0.06	7.70 ± 0.10	8.08 ± 0.13	7.73 ± 0.13	7.79 ± 0.15
Week 14	8.07 ± 0.05	8.11 ± 0.05	8.13 ± 0.05	8.13 ± 0.10	8.06 ± 0.09	7.97 ± 0.08
Reticulocytes (10^6/μL)						
Day 4	6.49 ± 0.32	6.40 ± 0.33	6.38 ± 0.26	6.13 ± 0.43	5.77 ± 0.34	4.52 ± 0.28**
Day 21	2.87 ± 0.16	3.04 ± 0.17	2.85 ± 0.14	2.90 ± 0.16	2.74 ± 0.10	2.88.± 0.16
Week 14	2.30 ± 0.08[b]	2.28 ± 0.03	2.16 ± 0.05	2.30 ± 0.08	2.21 ± 0.06	2.75 ± 0.08*
Mean cell volume (fL)						
Day 4	57.8 ± 0.3	57.8 ± 0.4	58.2 ± 0.3	57.5 ± 0.2	57.7 ± 0.3	56.7 ± 0.5
Day 21	57.9 ± 0.3	58.4 ± 0.5	58.4 ± 0.2	58.0 ± 0.5	57.2 ± 0.6	55.7 ± 0.3**
Week 14	52.5 ± 0.2	53.0 ± 0.2	52.6 ± 0.2	52.1 ± 0.2	51.5 ± 0.2*	51.3 ± 0.2**
Mean cell hemoglobin (pg)						
Day 4	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	19.0 ± 0.1	18.7 ± 0.1
Day 21	19.6 ± 0.1	19.7 ± 0.1	19.9 ± 0.1	19.5 ± 0.1	19.4 ± 0.1	18.9 ± 0.1**
Week 14	17.0 ± 0.1	17.1 ± 0.1	17.2 ± 0.1	17.0 ± 0.1	16.7 ± 0.1*	16.6 ± 0.1*
Mean cell hemoglobin concentration (g/dL)						
Day 4	32.8 ± 0.1	32.8 ± 0.2	32.7 ± 0.1	33.1 ± 0.2	33.0 ± 0.2	33.0 ± 0.2
Day 21	33.8 ± 0.1	33.7 ± 0.2	34.1 ± 0.1	33.6 ± 0.2	33.9 ± 0.2	33.9 ± 0.2
Week 14	32.4 ± 0.2	32.3 ± 0.3	32.6 ± 0.2	32.7 ± 0.2	32.5 ± 0.3	32.4 ± 0.2
Platelets (10^3/μL)						
Day 4	766.0 ± 19.4	802.3 ± 23.6	800.1 ± 24.8	794.9 ± 25.8	820.2 ± 21.1	744.6 ± 12.5
Day 21	722.9 ± 19.2	815.3 ± 24.9	803.8 ± 14.8	806.1 ± 25.1	754.4 ± 22.4	705.3 ± 19.8
Week 14	690.2 ± 15.6	661.5 ± 10.5	689.0 ± 15.4	674.7 ± 10.7	660.1 ± 13.9	608.2 ± 10.9**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Female (continued)						
Hematology (continued)						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	9	9	10
Week 14	10	10	10	10	10	10
Leukocytes (10^3/µL)						
Day 4	9.28 ± 0.33	9.82 ± 0.34	9.99 ± 0.53	9.61 ± 0.41	9.60 ± 0.34	9.55 ± 0.48
Day 21	9.95 ± 0.35	9.24 ± 0.52	9.52 ± 0.41	9.87 ± 0.66	9.46 ± 0.47	9.15 ± 0.35
Week 14	8.43 ± 0.23	8.06 ± 0.25	7.52 ± 0.32*	7.49 ± 0.45	6.70 ± 0.54**	6.97 ± 0.34**
Segmented neutrophils (10^3/µL)						
Day 4	1.08 ± 0.05	1.11 ± 0.06	1.15 ± 0.06	1.19 ± 0.08	1.22 ± 0.04	1.17 ± 0.14
Day 21	0.98 ± 0.07	0.92 ± 0.05	0.90 ± 0.04	1.09 ± 0.10	1.02 ± 0.06	1.13 ± 0.11
Week 14	1.41 ± 0.10	1.21 ± 0.06	1.18 ± 0.05	1.06 ± 0.08*	1.01 ± 0.08**	1.25 ± 0.08
Lymphocytes (10^3/µL)						
Day 4	7.73 ± 0.30	8.22 ± 0.33	8.32 ± 0.47	7.92 ± 0.33	7.87 ± 0.31	7.82 ± 0.40
Day 21	8.53 ± 0.29	7.87 ± 0.46	8.17 ± 0.37	8.31 ± 0.54	7.92 ± 0.40	7.52 ± 0.31
Week 14	6.31 ± 0.13	6.18 ± 0.24	5.69 ± 0.26	5.75 ± 0.34	5.00 ± 0.44**	5.00 ± 0.26**
Activated lymphocytes (10^3/µL)						
Day 4	0.29 ± 0.01	0.32 ± 0.03	0.34 ± 0.02	0.33 ± 0.03	0.35 ± 0.02	0.39 ± 0.02**
Day 21	0.29 ± 0.02	0.30 ± 0.03	0.30 ± 0.02	0.33 ± 0.03	0.38 ± 0.05	0.38 ± 0.03
Week 14	0.56 ± 0.06	0.53 ± 0.03	0.51 ± 0.04	0.55 ± 0.05	0.58 ± 0.05	0.61 ± 0.04
Monocytes (10^3/µL)						
Day 4	0.13 ± 0.01	0.12 ± 0.01	0.12 ± 0.02	0.13 ± 0.01	0.11 ± 0.01	0.10 ± 0.01
Day 21	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.06 ± 0.01
Week 14	0.09 ± 0.01	0.07 ± 0.00*	0.08 ± 0.01*	0.07 ± 0.01**	0.06 ± 0.00**	0.06 ± 0.01**
Basophils (10^3/µL)						
Day 4	0.011 ± 0.002	0.016 ± 0.002	0.016 ± 0.002	0.016 ± 0.002	0.016 ± 0.003	0.022 ± 0.004
Day 21	0.015 ± 0.002	0.015 ± 0.003	0.013 ± 0.002	0.014 ± 0.002	0.018 ± 0.004	0.013 ± 0.002
Week 14	0.018 ± 0.004	0.014 ± 0.002	0.009 ± 0.003	0.010 ± 0.003	0.010 ± 0.001	0.008 ± 0.002
Eosinophils (10^3/µL)						
Day 4	0.04 ± 0.00	0.04 ± 0.00	0.04 ± 0.00	0.03 ± 0.00	0.04 ± 0.01	0.04 ± 0.00
Day 21	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.00	0.05 ± 0.01	0.04 ± 0.00	0.05 ± 0.00
Week 14	0.05 ± 0.00	0.06 ± 0.00	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.00
Clinical Chemistry						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	8	9	10
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 4	10.2 ± 0.6	11.2 ± 0.3	11.1 ± 0.4	12.0 ± 0.4*	11.6 ± 0.5	12.5 ± 0.6**
Day 21	14.0 ± 0.3	13.5 ± 0.5	13.1 ± 0.5	13.0 ± 0.5	12.5 ± 0.3	14.1 ± 0.4
Week 14	13.0 ± 0.5	13.3 ± 0.5	13.8 ± 0.4	12.7 ± 0.4	12.8 ± 0.5	12.2 ± 0.5
Creatinine (mg/dL)						
Day 4	0.49 ± 0.01	0.49 ± 0.01	0.51 ± 0.01	0.49 ± 0.01	0.45 ± 0.02	0.48 ± 0.01
Day 21	0.48 ± 0.01	0.45 ± 0.02	0.45 ± 0.02	0.48 ± 0.02	0.44 ± 0.02	0.46 ± 0.02
Week 14	0.59 ± 0.01	0.59 ± 0.02	0.59 ± 0.01	0.63 ± 0.03	0.57 ± 0.02	0.57 ± 0.02
Total protein (g/dL)						
Day 4	5.6 ± 0.1	5.6 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.3 ± 0.1	5.2 ± 0.1*
Day 21	6.2 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	6.6 ± 0.1*	6.7 ± 0.1**	6.4 ± 0.1*
Week 14	6.7 ± 0.1	7.1 ± 0.1*	7.4 ± 0.1**	7.3 ± 0.1**	7.5 ± 0.1**	7.4 ± 0.1**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Female (continued)						
Clinical Chemistry (continued)						
Day 4	10	9	10	10	10	10
Day 21	10	10	10	8	9	10
Week 14	10	10	10	10	10	10
Albumin (g/dL)						
Day 4	4.1 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Day 21	4.6 ± 0.1	4.8 ± 0.1*	4.8 ± 0.1*	4.9 ± 0.1**	5.1 ± 0.1**	5.0 ± 0.1**
Week 14	5.2 ± 0.2	5.6 ± 0.1*	5.9 ± 0.1**	5.8 ± 0.1**	6.0 ± 0.1**	5.9 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 4	60 ± 5	63 ± 2	67 ± 2	69 ± 3	67 ± 7*	68 ± 6
Day 21	41 ± 3	36 ± 1**	38 ± 1*	38 ± 1*	29 ± 2**	32 ± 2**
Week 14	40 ± 1	40 ± 2	37 ± 1	35 ± 2	34 ± 3**	36 ± 3*
Alkaline phosphatase (IU/L)						
Day 4	550 ± 13	596 ± 24	582 ± 15	642 ± 25**	674 ± 31**	613 ± 26**
Day 21	374 ± 10	355 ± 8	341 ± 12*	356 ± 10	317 ± 9**	302 ± 10**
Week 14	165 ± 8	162 ± 7	162 ± 6	152 ± 5	149 ± 5	142 ± 6*
Creatine kinase (IU/L)						
Day 4	646 ± 33	635 ± 33	603 ± 36	750 ± 53	629 ± 32	631 ± 33
Day 21	530 ± 74	449 ± 28	477 ± 62	475 ± 35[b]	440 ± 30	473 ± 39
Week 14	287 ± 32	212 ± 25	250 ± 30	253 ± 19	220 ± 25	187 ± 21
Sorbitol dehydrogenase (IU/L)						
Day 4	7 ± 0	7 ± 1	8 ± 0	8 ± 1	9 ± 1*	8 ± 1*
Day 21	8 ± 0	8 ± 0	8 ± 1	8 ± 0[b]	9 ± 0*	9 ± 0**
Week 14	7 ± 0	7 ± 0	8 ± 0	8 ± 0	8 ± 0	8 ± 1
Bile acids (μmol/L)						
Day 4	21.5 ± 2.0	22.9 ± 2.2	25.1 ± 2.1	25.9 ± 1.9	32.9 ± 3.3**	44.8 ± 4.8**
Day 21	24.0 ± 2.4	17.5 ± 0.9*	20.3 ± 1.2	20.4 ± 1.6	18.2 ± 0.9	18.1 ± 0.7
Week 14	22.9 ± 2.1	25.6 ± 2.9	20.7 ± 2.7	22.5 ± 2.8	23.0 ± 3.1	24.9 ± 2.8

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F2
Hematology Data for Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
Male						
n	10	10	10	10	9	10
Hematocrit (%)	48.5 ± 0.7	48.7 ± 0.7	48.7 ± 0.9	49.5 ± 0.7	51.0 ± 1.1	49.9 ± 0.8
Hemoglobin (g/dL)	16.7 ± 0.2	16.6 ± 0.2	16.5 ± 0.3	16.7 ± 0.3	17.1 ± 0.3	16.8 ± 0.3
Erythrocytes (10^6/µL)	10.97 ± 0.15	10.93 ± 0.16	10.99 ± 0.21	11.09 ± 0.18	11.46 ± 0.24	11.39 ± 0.17
Reticulocytes (10^6/µL)	3.97 ± 0.10[b]	3.94 ± 0.09	3.94 ± 0.11	4.02 ± 0.09	4.14 ± 0.12	4.37 ± 0.12*[b]
Mean cell volume (fL)	44.2 ± 0.1	44.6 ± 0.2	44.4 ± 0.2	44.6 ± 0.1	44.5 ± 0.2	43.8 ± 0.1
Mean cell hemoglobin (pg)	15.2 ± 0.1	15.2 ± 0.1	15.0 ± 0.1	15.1 ± 0.1	15.0 ± 0.1	14.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.2	34.0 ± 0.1	33.9 ± 0.2	33.7 ± 0.1**	33.6 ± 0.2**	33.8 ± 0.2**
Platelets (10^3/µL)	844.9 ± 49.3	859.5 ± 20.1	848.7 ± 33.6	819.2 ± 44.2	716.0 ± 67.6	712.9 ± 51.4*
Leukocytes (10^3/µL)	6.90 ± 0.32	5.85 ± 0.28	5.71 ± 0.34	5.58 ± 0.50	5.90 ± 0.45	5.32 ± 0.45*
Segmented neutrophils (10^3/µL)	0.90 ± 0.11	0.68 ± 0.04*	0.61 ± 0.07*	0.59 ± 0.05**	0.68 ± 0.11**	0.54 ± 0.08
Lymphocytes (10^3/µL)	5.79 ± 0.25	5.02 ± 0.25	4.97 ± 0.29	4.84 ± 0.44	5.08 ± 0.38	4.64 ± 0.37
Activated lymphocytes (10^3/µL)	0.07 ± 0.01	0.06 ± 0.00	0.06 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
Monocytes (10^3/µL)	0.07 ± 0.01	0.05 ± 0.01	0.04 ± 0.00*	0.05 ± 0.00	0.05 ± 0.01	0.05 ± 0.01
Basophils (10^3/µL)	0.004 ± 0.002	0.004 ± 0.002	0.005 ± 0.002	0.003 ± 0.002	0.004 ± 0.002	0.005 ± 0.002
Eosinophils (10^3/µL)	0.06 ± 0.03	0.03 ± 0.01	0.02 ± 0.01[b]	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
Female						
n	10	10	10	10	10	10
Hematocrit (%)	50.4 ± 0.4	49.6 ± 0.5	47.9 ± 0.7	50.6 ± 0.9	50.4 ± 1.0	50.5 ± 1.0
Hemoglobin (g/dL)	16.4 ± 0.1	16.0 ± 0.2	15.6 ± 0.2	16.5 ± 0.2	16.6 ± 0.3	16.5 ± 0.2
Erythrocytes (10^6/µL)	10.47 ± 0.09	10.24 ± 0.14	9.96 ± 0.14	10.55 ± 0.18	10.46 ± 0.19	10.51 ± 0.19
Reticulocytes (10^6/µL)	3.37 ± 0.13	3.12 ± 0.17	3.26 ± 0.12[b]	3.37 ± 0.12[b]	3.42 ± 0.18[b]	3.81 ± 0.14
Mean cell volume (fL)	48.1 ± 0.2	48.4 ± 0.3	48.1 ± 0.2	48.0 ± 0.2	48.2 ± 0.2	48.1 ± 0.2
Mean cell hemoglobin (pg)	15.6 ± 0.1	15.7 ± 0.1	15.7 ± 0.1	15.6 ± 0.1	15.8 ± 0.1	15.7 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.4 ± 0.2	32.7 ± 0.2	32.6 ± 0.2	32.9 ± 0.2	32.7 ± 0.3
Platelets (10^3/µL)	767.0 ± 26.9	853.2 ± 44.5	906.1 ± 38.2	788.3 ± 48.2	648.0 ± 54.1	663.8 ± 49.6
Leukocytes (10^3/µL)	4.56 ± 0.48	4.30 ± 0.37	3.56 ± 0.48	4.31 ± 0.30	3.78 ± 0.32	4.46 ± 0.55
Segmented neutrophils (10^3/µL)	0.54 ± 0.06	0.47 ± 0.04	0.43 ± 0.07	0.47 ± 0.07	0.34 ± 0.04	0.48 ± 0.08
Lymphocytes (10^3/µL)	3.81 ± 0.41	3.63 ± 0.31	2.93 ± 0.42	3.62 ± 0.23	3.25 ± 0.28	3.76 ± 0.46
Activated lymphocytes (10^3/µL)	0.10 ± 0.01	0.11 ± 0.01	0.12 ± 0.02	0.11 ± 0.01	0.10 ± 0.01	0.12 ± 0.02
Monocytes (10^3/µL)	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.03 ± 0.00
Basophils (10^3/µL)	0.000 ± 0.000	0.003 ± 0.002	0.000 ± 0.000	0.003 ± 0.002	0.002 ± 0.001	0.006 ± 0.002**
Eosinophils (10^3/µL)	0.07 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.07 ± 0.01	0.05 ± 0.01	0.07 ± 0.01

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
**$P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

APPENDIX G
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	5	5	5	5	5	5
Male						
Necropsy body weight	161 ± 4	169 ± 6	167 ± 8	167 ± 5	171 ± 4	166 ± 5
Heart						
Absolute	0.594 ± 0.014	0.560 ± 0.021	0.576 ± 0.024	0.556 ± 0.007	0.566 ± 0.015	0.508 ± 0.020*
Relative	3.693 ± 0.035	3.307 ± 0.029**	3.468 ± 0.082**	3.337 ± 0.080**	3.309 ± 0.081**	3.055 ± 0.040**
R. Kidney						
Absolute	0.690 ± 0.030	0.762 ± 0.047	0.776 ± 0.044	0.790 ± 0.020	0.814 ± 0.019*	0.780 ± 0.017
Relative	4.287 ± 0.138	4.489 ± 0.150	4.656 ± 0.076	4.739 ± 0.134*	4.757 ± 0.059*	4.706 ± 0.108
Liver						
Absolute	7.520 ± 0.070	9.246 ± 0.509**	8.882 ± 0.364**	9.870 ± 0.311**	10.486 ± 0.253**	10.474 ± 0.436**
Relative	46.843 ± 1.043	54.545 ± 1.807**	53.603 ± 2.171**	59.080 ± 0.537**	61.342 ± 1.696**	62.987 ± 1.014**
Lung						
Absolute	1.112 ± 0.107	1.114 ± 0.123	1.046 ± 0.068	0.948 ± 0.014	1.150 ± 0.129	0.884 ± 0.046
Relative	6.891 ± 0.584	6.634 ± 0.828	6.268 ± 0.172	5.693 ± 0.174	6.674 ± 0.610	5.326 ± 0.239
R. Testis						
Absolute	1.005 ± 0.030	1.002 ± 0.018	1.006 ± 0.038	0.956 ± 0.043	0.944 ± 0.036	0.891 ± 0.038
Relative	6.250 ± 0.157	5.937 ± 0.150	6.059 ± 0.126	5.730 ± 0.267*	5.511 ± 0.097**	5.362 ± 0.121**
Thymus						
Absolute	0.380 ± 0.016	0.392 ± 0.012	0.363 ± 0.008	0.382 ± 0.014	0.369 ± 0.024	0.339 ± 0.007
Relative	2.372 ± 0.123	2.320 ± 0.050	2.196 ± 0.070	2.290 ± 0.065	2.155 ± 0.119	2.046 ± 0.050*
Female						
Necropsy body weight	120 ± 3	121 ± 2	129 ± 2	125 ± 3	118 ± 4	124 ± 4
Heart						
Absolute	0.458 ± 0.017	0.442 ± 0.011	0.480 ± 0.016	0.438 ± 0.008	0.408 ± 0.016	0.430 ± 0.016
Relative	3.811 ± 0.148	3.642 ± 0.081	3.726 ± 0.094	3.509 ± 0.077*	3.448 ± 0.048*	3.468 ± 0.064*
R. Kidney						
Absolute	0.532 ± 0.021	0.582 ± 0.024	0.598 ± 0.017	0.602 ± 0.026	0.550 ± 0.022	0.600 ± 0.020
Relative	4.419 ± 0.116	4.787 ± 0.124	4.645 ± 0.110	4.806 ± 0.088	4.653 ± 0.143	4.852 ± 0.163
Liver						
Absolute	5.148 ± 0.158	5.812 ± 0.255*	6.518 ± 0.148**	6.392 ± 0.196**	6.258 ± 0.268**	7.430 ± 0.232**
Relative	42.783 ± 0.708	47.819 ± 1.574**	50.632 ± 0.908**	51.104 ± 0.497**	52.862 ± 0.815**	59.969 ± 0.640**
Lung						
Absolute	0.936 ± 0.103	0.920 ± 0.065	0.864 ± 0.046	0.770 ± 0.024	0.850 ± 0.057	0.752 ± 0.025
Relative	7.849 ± 1.020	7.593 ± 0.567	6.712 ± 0.347	6.172 ± 0.223	7.189 ± 0.435	6.075 ± 0.156
Thymus						
Absolute	0.319 ± 0.015	0.335 ± 0.015	0.340 ± 0.011	0.303 ± 0.006	0.302 ± 0.009	0.293 ± 0.007
Relative	2.649 ± 0.086	2.760 ± 0.100	2.638 ± 0.085	2.436 ± 0.097	2.558 ± 0.052	2.364 ± 0.035*

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10	10	10
Male						
Necropsy body weight	333 ± 5	345 ± 6	350 ± 4	348 ± 4	346 ± 6	311 ± 3*
Heart						
Absolute	0.867 ± 0.013	0.870 ± 0.012	0.870 ± 0.009	0.853 ± 0.016	0.868 ± 0.019	0.773 ± 0.012**
Relative	2.609 ± 0.040	2.527 ± 0.033	2.488 ± 0.031*	2.454 ± 0.031**	2.509 ± 0.022	2.485 ± 0.028*
R. Kidney						
Absolute	1.018 ± 0.023	1.097 ± 0.032*	1.076 ± 0.023	1.125 ± 0.023**	1.173 ± 0.020**	1.162 ± 0.021**
Relative	3.062 ± 0.063	3.177 ± 0.043	3.072 ± 0.038	3.236 ± 0.044*	3.394 ± 0.044**	3.737 ± 0.063**
Liver						
Absolute	10.737 ± 0.370	12.334 ± 0.319**	13.273 ± 0.323**	13.282 ± 0.238**	14.186 ± 0.384**	15.032 ± 0.307**
Relative	32.306 ± 1.125	35.734 ± 0.369**	37.935 ± 0.879**	38.218 ± 0.464**	41.013 ± 0.819**	48.321 ± 0.812**
Lung						
Absolute	1.382 ± 0.034	1.402 ± 0.035	1.477 ± 0.064	1.393 ± 0.040	1.398 ± 0.027	1.307 ± 0.038
Relative	4.165 ± 0.134	4.063 ± 0.046	4.229 ± 0.202	4.007 ± 0.095	4.045 ± 0.061	4.197 ± 0.092
R. Testis						
Absolute	1.421 ± 0.014	1.442 ± 0.022	1.411 ± 0.028	1.444 ± 0.026	1.414 ± 0.018	0.682 ± 0.078**
Relative	4.279 ± 0.067	4.190 ± 0.070	4.033 ± 0.073	4.158 ± 0.078	4.092 ± 0.046	2.193 ± 0.250**
Thymus						
Absolute	0.266 ± 0.014	0.242 ± 0.010	0.249 ± 0.006	0.258 ± 0.010	0.263 ± 0.014	0.214 ± 0.008**
Relative	0.802 ± 0.046	0.702 ± 0.029	0.712 ± 0.021	0.744 ± 0.035	0.760 ± 0.035	0.688 ± 0.022
Female						
Necropsy body weight	196 ± 3	193 ± 3	196 ± 2	191 ± 3	190 ± 3	170 ± 2**
Heart						
Absolute	0.568 ± 0.019	0.562 ± 0.008	0.565 ± 0.013	0.567 ± 0.009	0.560 ± 0.008	0.509 ± 0.008**
Relative	2.903 ± 0.094	2.918 ± 0.043	2.883 ± 0.040	2.972 ± 0.052	2.957 ± 0.038	2.994 ± 0.043
R. Kidney						
Absolute	0.651 ± 0.010	0.665 ± 0.011	0.669 ± 0.012	0.697 ± 0.013*	0.734 ± 0.010**	0.714 ± 0.015**
Relative	3.328 ± 0.046	3.450 ± 0.042	3.417 ± 0.051	3.649 ± 0.049**	3.876 ± 0.045**	4.197 ± 0.063**
Liver						
Absolute	6.099 ± 0.149	6.544 ± 0.132*	7.366 ± 0.117**	7.479 ± 0.141**	7.917 ± 0.171**	8.188 ± 0.156**
Relative	31.158 ± 0.626	33.946 ± 0.494**	37.608 ± 0.306**	39.141 ± 0.350**	41.746 ± 0.407**	48.141 ± 0.716**
Lung						
Absolute	1.000 ± 0.023	0.949 ± 0.022	0.999 ± 0.026	0.952 ± 0.022	0.975 ± 0.028	0.903 ± 0.020*
Relative	5.121 ± 0.151	4.928 ± 0.118	5.096 ± 0.086	4.986 ± 0.100	5.138 ± 0.096	5.312 ± 0.113
Thymus						
Absolute	0.218 ± 0.006	0.199 ± 0.005	0.211 ± 0.007	0.207 ± 0.003	0.195 ± 0.006**	0.174 ± 0.003**
Relative	1.113 ± 0.023	1.034 ± 0.032	1.077 ± 0.032	1.085 ± 0.018	1.025 ± 0.024	1.024 ± 0.017

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	5	5	5	5	5	5
Male						
Necropsy body weight	25.2 ± 0.4	24.4 ± 0.6	25.5 ± 0.4	26.4 ± 0.4	25.7 ± 0.3	24.5 ± 0.4
Heart						
Absolute	0.128 ± 0.006	0.126 ± 0.004	0.126 ± 0.002	0.126 ± 0.002	0.120 ± 0.004	0.114 ± 0.002
Relative	5.096 ± 0.264	5.154 ± 0.078	4.957 ± 0.154	4.784 ± 0.118	4.676 ± 0.207	4.653 ± 0.106
R. Kidney						
Absolute	0.248 ± 0.011	0.242 ± 0.009	0.252 ± 0.006	0.246 ± 0.004	0.252 ± 0.006	0.222 ± 0.007
Relative	9.864 ± 0.462	9.896 ± 0.191	9.907 ± 0.268	9.340 ± 0.207	9.810 ± 0.245	9.067 ± 0.352
Liver						
Absolute	1.308 ± 0.022	1.240 ± 0.070	1.344 ± 0.032	1.420 ± 0.044	1.498 ± 0.060*	1.624 ± 0.048**
Relative	52.092 ± 1.683	50.604 ± 1.837	52.834 ± 1.441	53.929 ± 1.974	58.351 ± 2.575	66.362 ± 2.626**
Lung						
Absolute	0.170 ± 0.003	0.156 ± 0.005	0.174 ± 0.010	0.160 ± 0.004	0.176 ± 0.005	0.156 ± 0.002
Relative	6.763 ± 0.160	6.381 ± 0.124	6.834 ± 0.386	6.078 ± 0.219	6.853 ± 0.224	6.373 ± 0.181
R. Testis						
Absolute	0.102 ± 0.004	0.103 ± 0.002	0.095 ± 0.004	0.102 ± 0.002	0.106 ± 0.001	0.096 ± 0.002
Relative	4.057 ± 0.107	4.237 ± 0.094	3.737 ± 0.109	3.879 ± 0.072	4.121 ± 0.094	3.916 ± 0.071
Thymus						
Absolute	0.048 ± 0.002	0.047 ± 0.003	0.040 ± 0.006	0.043 ± 0.003	0.034 ± 0.003**	0.031 ± 0.002**
Relative	1.896 ± 0.095	1.906 ± 0.107	1.580 ± 0.238	1.646 ± 0.096	1.310 ± 0.118**	1.276 ± 0.091**
Female						
Necropsy body weight	20.5 ± 0.4	20.5 ± 0.3	20.6 ± 0.3	21.0 ± 0.4	21.4 ± 0.3	20.9 ± 0.4
Heart						
Absolute	0.104 ± 0.002	0.102 ± 0.004	0.110 ± 0.005	0.110 ± 0.003	0.112 ± 0.004	0.104 ± 0.004
Relative	5.068 ± 0.132	4.988 ± 0.191	5.337 ± 0.214	5.240 ± 0.135	5.229 ± 0.167	4.975 ± 0.195
R. Kidney						
Absolute	0.154 ± 0.004	0.158 ± 0.004	0.162 ± 0.007	0.160 ± 0.004	0.164 ± 0.004	0.170 ± 0.005
Relative	7.501 ± 0.169	7.725 ± 0.182	7.861 ± 0.265	7.616 ± 0.106	7.657 ± 0.163	8.131 ± 0.261
Liver						
Absolute	1.004 ± 0.007	0.994 ± 0.022	1.026 ± 0.040	1.136 ± 0.048*	1.198 ± 0.049**	1.302 ± 0.034**
Relative	48.952 ± 1.037	48.636 ± 1.410	49.802 ± 1.437	54.011 ± 1.385*	55.868 ± 1.761**	62.200 ± 0.662**
Lung						
Absolute	0.150 ± 0.006	0.156 ± 0.007	0.152 ± 0.007	0.146 ± 0.002	0.152 ± 0.008	0.180 ± 0.025
Relative	7.295 ± 0.212	7.622 ± 0.308	7.378 ± 0.260	6.955 ± 0.076	7.097 ± 0.366	8.596 ± 1.189
Thymus						
Absolute	0.065 ± 0.005	0.058 ± 0.002	0.056 ± 0.006	0.057 ± 0.003	0.052 ± 0.003*	0.047 ± 0.001**
Relative	3.155 ± 0.192	2.838 ± 0.119	2.720 ± 0.279	2.713 ± 0.099	2.430 ± 0.150**	2.229 ± 0.047**

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	125 mg/L	250 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10	10	10
Male						
Necropsy body weight	39.4 ± 1.2	40.3 ± 0.7	40.9 ± 0.5	41.1 ± 0.9	38.9 ± 1.0	36.2 ± 1.2
Heart						
Absolute	0.152 ± 0.002	0.165 ± 0.004	0.168 ± 0.004	0.160 ± 0.007	0.145 ± 0.004	0.138 ± 0.004*
Relative	3.882 ± 0.114	4.101 ± 0.071	4.111 ± 0.101	3.891 ± 0.135	3.744 ± 0.130	3.842 ± 0.163
R. Kidney						
Absolute	0.297 ± 0.007	0.286 ± 0.003	0.305 ± 0.006	0.297 ± 0.005	0.293 ± 0.008	0.286 ± 0.004
Relative	7.588 ± 0.259	7.122 ± 0.139	7.462 ± 0.149	7.251 ± 0.170	7.556 ± 0.197	7.985 ± 0.305
Liver						
Absolute	1.630 ± 0.059	1.760 ± 0.048	1.795 ± 0.047	1.835 ± 0.076*	1.873 ± 0.065**	2.097 ± 0.064**
Relative	41.363 ± 0.898	43.726 ± 0.896	43.863 ± 0.956	44.545 ± 1.116	48.202 ± 1.418**	58.280 ± 1.979**
Lung						
Absolute	0.294 ± 0.011	0.303 ± 0.003	0.301 ± 0.009	0.297 ± 0.013	0.286 ± 0.015	0.296 ± 0.014
Relative	7.515 ± 0.348	7.549 ± 0.156	7.366 ± 0.234	7.258 ± 0.340	7.394 ± 0.467	8.319 ± 0.581
R. Testis						
Absolute	0.121 ± 0.002	0.121 ± 0.003	0.126 ± 0.002	0.123 ± 0.001	0.118 ± 0.003	0.115 ± 0.002
Relative	3.093 ± 0.108	2.981 ± 0.048	3.089 ± 0.064	2.994 ± 0.073	3.052 ± 0.116	3.196 ± 0.100
Thymus						
Absolute	0.041 ± 0.002	0.041 ± 0.002	0.042 ± 0.002	0.040 ± 0.003	0.038 ± 0.002	0.035 ± 0.002
Relative	1.030 ± 0.033	1.028 ± 0.065	1.071 ± 0.062	0.970 ± 0.069	0.977 ± 0.056	0.975 ± 0.037
Female						
Necropsy body wt	30.5 ± 1.0	30.6 ± 1.1	31.6 ± 0.9	31.0 ± 1.1	31.0 ± 0.4	27.4 ± 0.7
Heart						
Absolute	0.123 ± 0.004	0.126 ± 0.003	0.122 ± 0.004	0.123 ± 0.003	0.123 ± 0.003	0.117 ± 0.002
Relative	4.049 ± 0.127	4.147 ± 0.103	3.880 ± 0.140	4.021 ± 0.172	3.975 ± 0.101	4.298 ± 0.111
R. Kidney						
Absolute	0.182 ± 0.006	0.185 ± 0.003	0.189 ± 0.006	0.190 ± 0.005	0.193 ± 0.006	0.191 ± 0.005
Relative	5.984 ± 0.183	6.109 ± 0.190	6.004 ± 0.190	6.165 ± 0.147	6.225 ± 0.165	7.034 ± 0.290**
Liver						
Absolute	1.191 ± 0.050	1.236 ± 0.067	1.346 ± 0.058	1.390 ± 0.051*	1.551 ± 0.043**	1.670 ± 0.063**
Relative	39.111 ± 1.371	40.284 ± 1.023	42.544 ± 1.173	45.050 ± 1.465**	50.031 ± 1.196**	61.041 ± 1.571**
Lung						
Absolute	0.213 ± 0.008	0.214 ± 0.012	0.200 ± 0.013	0.240 ± 0.009	0.260 ± 0.013*	0.247 ± 0.013*
Relative	7.052 ± 0.370	7.121 ± 0.538	6.390 ± 0.443	7.822 ± 0.362	8.389 ± 0.415*	9.097 ± 0.540**
Thymus						
Absolute	0.045 ± 0.002	0.039 ± 0.002	0.046 ± 0.002	0.043 ± 0.003	0.049 ± 0.002	0.037 ± 0.002
Relative	1.478 ± 0.075	1.292 ± 0.080	1.470 ± 0.066	1.401 ± 0.070	1.589 ± 0.063	1.365 ± 0.066

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX H
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10
Weights (g)				
Necropsy body weight	333 ± 5	348 ± 4	346 ± 6	311 ± 3**
L. Cauda	0.1603 ± 0.0062	0.1541 ± 0.0053	0.1671 ± 0.0064	0.1015 ± 0.0069**
L. Epididymis	0.5124 ± 0.0138	0.5067 ± 0.0114	0.5416 ± 0.0197	0.3363 ± 0.0160**
L. Testis	1.5090 ± 0.0174	1.5810 ± 0.0194	1.5455 ± 0.0198	0.7008 ± 0.0706**
Spermatid measurements				
Spermatid heads (10^7/g testis)	122.71 ± 4.36	135.36 ± 4.43	140.10 ± 5.77	26.44 ± 14.75*
Spermatid heads (10^7/testis)	168.50 ± 6.70	193.00 ± 5.26	198.13 ± 8.34	24.94 ± 14.83*
Spermatid heads (10^7/cauda)	112.64 ± 7.24	102.52 ± 7.29	106.67 ± 5.37	0.47 ± 0.29**
Epididymal spermatozoal measurements				
Motility (%)	75.41 ± 1.14	76.10 ± 2.22	75.76 ± 1.82	13.09 ± 8.80**
Concentration (10^7/g cauda epididymal tissue)	708 ± 46	673 ± 55	650 ± 49	4 ± 3**

* Significantly different (P≤0.05) from the control group by Dunn's test
** Significantly different (P≤0.01) from the control group by Dunnett's (body weights), Williams' (tissue weights), or Shirley's (epididymal spermatozoal measurements) test
[a] Data are presented as mean ± standard error.

TABLE H2
Estrous Cycle Length for Female Rats in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10
Necropsy body wt	196 ± 3	192 ± 3	190 ± 3	170 ± 2**
Estrous cycle length (days)	4.55 ± 0.16	4.90 ± 0.07	4.85 ± 0.17	5.00 ± 0.00*

* Significantly different (P≤0.05) from the control group by Dunn's test (estrous cycle length)
** Significantly different (P≤0.01) from the control group by Williams' test (body weight)
[a] Data are presented as mean ± standard error.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10
Weights (g)				
Necropsy body weight	39.4 ± 1.2	41.1 ± 0.9	38.9 ± 1.0	36.2 ± 1.2
L. Cauda	0.0277 ± 0.0011	0.0274 ± 0.0011	0.0275 ± 0.0013	0.0260 ± 0.0014
L. Epididymis	0.0585 ± 0.0020	0.0615 ± 0.0034	0.0593 ± 0.0019	0.0553 ± 0.0028
L. Testis	0.1188 ± 0.0022	0.1259 ± 0.0018*	0.1191 ± 0.0026	0.1144 ± 0.0014
Spermatid measurements				
Spermatid heads (10^7/g testis)	201.47 ± 5.97	173.67 ± 7.03*	188.94 ± 5.29	190.43 ± 8.79
Spermatid heads (10^7/testis)	22.31 ± 0.74	20.14 ± 0.75	20.65 ± 0.71	20.23 ± 0.94
Spermatid heads (10^7/cauda)	21.66 ± 2.69	21.49 ± 1.16	21.56 ± 1.20	19.79 ± 2.18
Epididymal spermatozoal measurements				
Motility (%)	69.51 ± 1.88	70.50 ± 2.43	69.47 ± 2.19	63.80 ± 2.66
Concentration (10^7/g cauda epididymal tissue)	802 ± 102	791 ± 47	804 ± 66	806 ± 132

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's (tissue weights) or Dunn's (spermatid measurements) test
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunn's test (epididymal spermatozoal measurements).

TABLE H4
Estrous Cycle Length for Female Mice in the 3-Month Drinking Water Study of Dibromoacetic Acid[a]

	0 mg/L	500 mg/L	1,000 mg/L	2,000 mg/L
n	10	10	10	10
Necropsy body wt	31 ± 1	31 ± 1	31 ± 0	27 ± 1*
Estrous cycle length (days)	4.67 ± 0.50	5.09 ± 0.75	4.28 ± 0.25	4.35 ± 0.21

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test.

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Dibromoacetic Acid

Dibromoacetic acid was obtained from Fluka (Buchs, Switzerland) in one lot (46019/1 55196). Lot 46019/1 55196 was used in the 2-week, 3-month, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory at Battelle Columbus Operations (Columbus, OH) and by the study laboratory at Southern Research Institute (Birmingham, AL). Karl Fischer titration, elemental analysis, and melting point determination were performed by Galbraith Laboratories, Inc. (Knoxville, TN).

The chemical, a clumped white powder or moist white crystalline solid, was identified as dibromoacetic acid by the study laboratory using infrared spectroscopy and by the anlytical chemistry laboratory using infrared, ultraviolet/visible, and proton and carbon-13 nuclear magnetic resonance spectroscopy. In addition, the study laboratory made a comparison of infrared and proton nuclear magnetic resonance spectra to that of a frozen reference from the same lot and a reference sample manufactured by Aldrich Chemical Co. (Milwaukee, WI). All spectra were consistent with the literature spectra for dibromoacetic acid (*Aldrich*, 1985, 1992). Representative infrared and proton and nuclear magnetic resonance spectra are presented in Figures I1, I2, and I3.

The purity of lot 46019/1 55196 was determined by the analytical chemistry laboratory using functional group titration, ion chromatography, and high performance liquid chromatography (HPLC) and by the study laboratory using HPLC. HPLC (Waters Corporation, Milford, MA) was performed with a Prodigy 5 ODS-3, 150 mm × 4.6 mm, (5-µm particle size) column (Phenomenex, Torrence, CA), an Inertsil ODS-2 guard cartridge, and an ultraviolet detector at 220 nm; mobile phases A: 15 mM phosphoric acid and B: 30 mM phosphoric acid:acetonitrile (1:1), at a flow rate of 1 mL/minute; beginning with 100% A linear to 100% B in 20 minutes (19 minutes for stability analysis; 5 minutes for standard addition), held 15 minutes, then linear to 100% A in 5 minutes, held 25 minutes (20 minutes for stability analysis; 10 minutes for standard addition). Ion chromatography (IC) (Dionex, Sunnyvale, CA) was performed using an Ionpac As11 column (250 mm × 4 mm), an Ionpac As11 guard column (50 mm), mobile phases of A: 4mM sodium hydroxide and B: 32 mM sodium hydroxide, with a flow rate of 1.5 mL/minute, and a suppressed conductivity detector. The mobile phase gradient was held at 100% A for 9.9 minutes, then linear to 100% B in 6 seconds, held 13.9 minutes, then linear to 100% A in 6 seconds, and held for 2 minutes.

Karl Fischer titration indicated 0.27% water. Elemental analyses for carbon, hydrogen, and bromine were in agreement with the theoretical values for dibromoacetic acid. The melting point determination was slightly higher (38.6° C) than that given by the manufacturer's certificate of analysis and Material Safety Data Sheet (32° to 38° C); no reference was found in the literature. Functional group titration indicated a purity of greater than 100%, which was consistent with the manufacturer's certificate of analysis. IC indicated one major peak and two impurites with a combined area of 3.4% (3.2% and 0.2%). Using HPLC and standard addition, the 3.2% impurity was found to have the same retention time as monobromoacetic acid; comparison with HPLC results (0.4%) suggest that IC results may overestimate the amount of monobromoacetic acid. HPLC indicated one major peak and one impurity with a relative peak area of 0.34%. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using HPLC. These studies indicated that dibromoacetic acid was stable for up to 15 days when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in sealed amber glass containers.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once during the 2-week studies, four times during the 3-month studies, and approximately every 2 weeks throughout the 2-year studies. The dose formulations were prepared by mixing dibromoacetic acid with tap water (Table I1). Formulations were adjusted to pH 5 with 1 N sodium hydroxide and stored in sealed opaque glass or Nalgene® containers at 5° C for at least 42 days.

Homogeneity studies of 125 and 2,000 mg/mL formulations were conducted by the study laboratory, and stability studies of a 10 µg/mL formulation (pH 5) were conducted by the analytical study laboratory using IC by the system previously described except for a change to an isocratic mobile phase of 4mM sodium hydroxide for 25 minutes. Homogeneity was confirmed, and stability was confirmed for at least 42 days when stored at 5° C in sealed opaque glass or Nalgene® containers, and at animal room conditions for at least 3 days.

Periodic analyses of the dose formulations of dibromoacetic acid were conducted by the study laboratory using IC according to the previously described method. During the 2-week studies, the dose formulations were analyzed once; all five of the dose formulations for rats and mice were within 10% of the target concentrations, with no value more than 10% greater than the target concentration (Table I2). Animal room samples of these dose formulations were also analyzed; all 23 samples analyzed were within 10% of the target concentrations. During the 3-month studies, the dose formulations were analyzed at the beginning, midpoint, and end of the studies; all 20 of the dose formulations used for rats and mice were within 10% of the target concentrations, with no value more than 9% greater than the target concentration (Table I3). Animal room samples of these dose formulations were also analyzed; 26 of 30 samples were within 10% of the target concentrations. During the 2-year studies, the dose formulations were analyzed approximately every 7 to 8 weeks (Table I4). All 34 of the dose formulations analyzed were within 10% of the target concentrations. Animal room samples of these dose formulations were also analyzed; 23 of 24 samples were within 10% of the target concentrations.

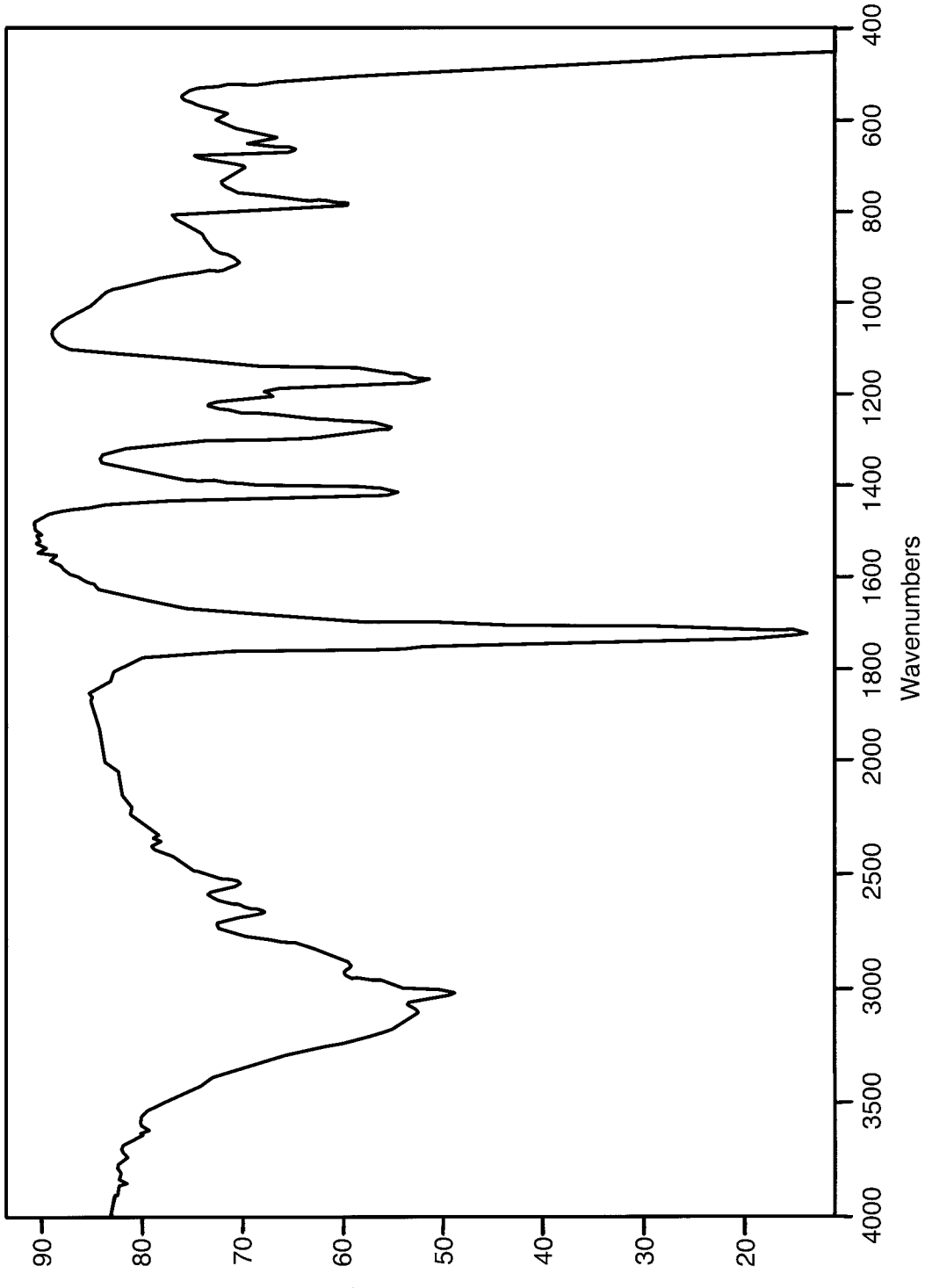

FIGURE I1
Infrared Absorption Spectrum of Dibromoacetic Acid

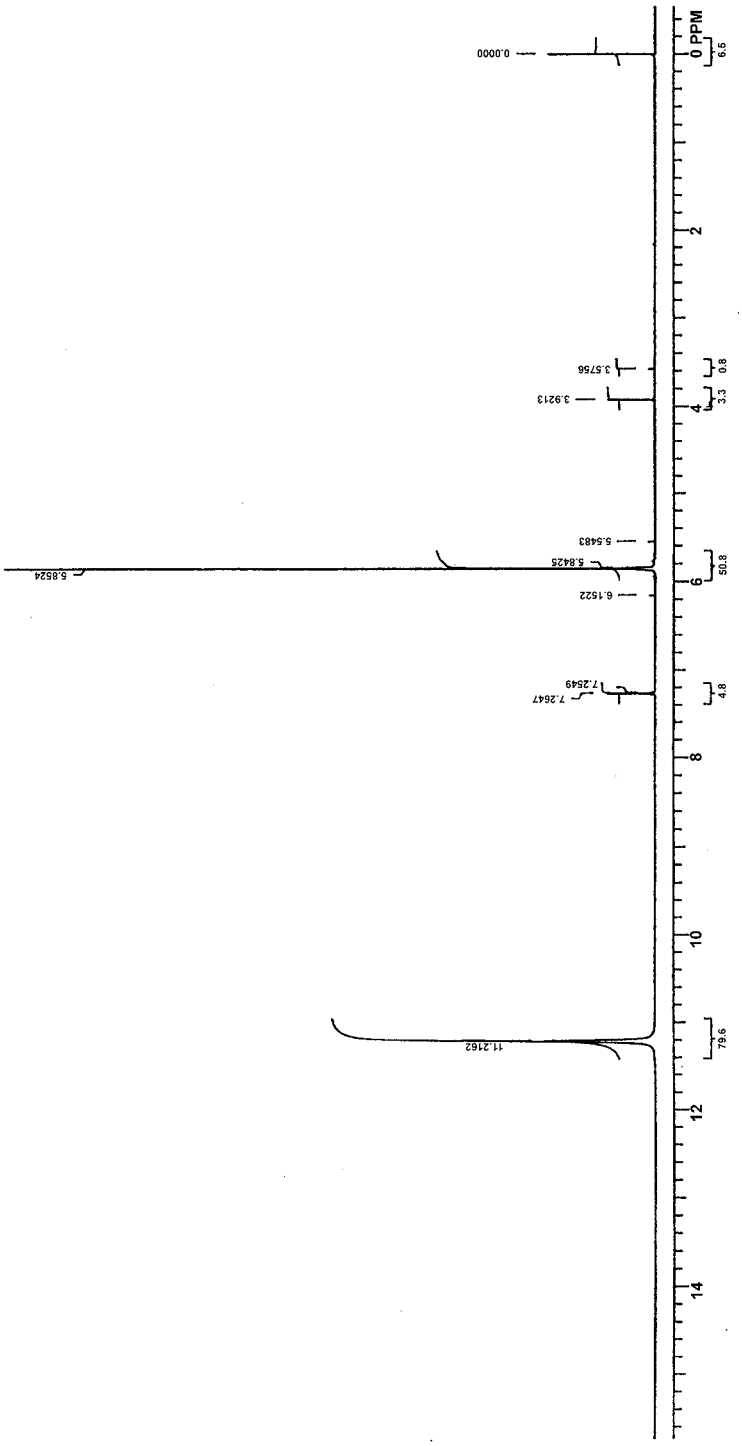

FIGURE I2
Proton Nuclear Magnetic Resonance Spectrum of Dibromoacetic Acid

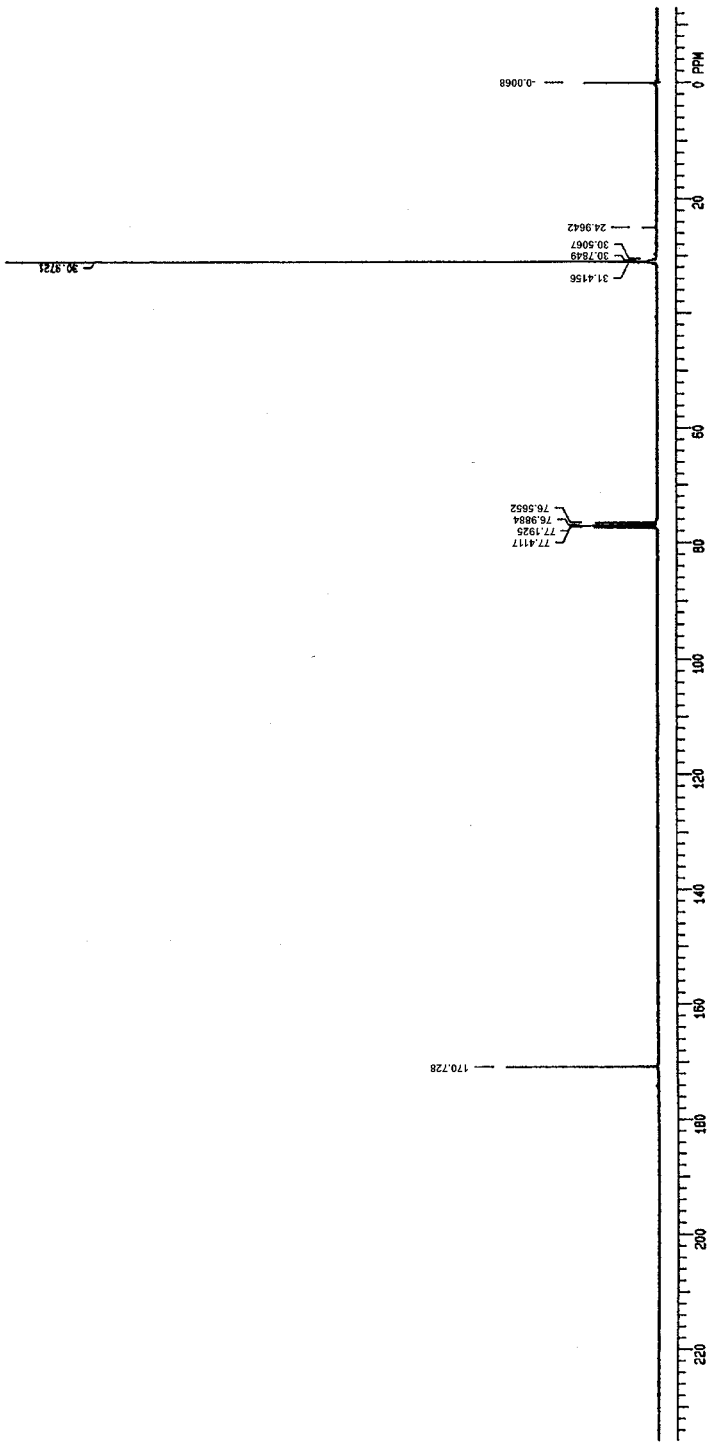

FIGURE I3
Carbon-13 Nuclear Magnetic Resonance Spectrum of Dibromoacetic Acid

TABLE I1
Preparation and Storage of Dose Formulations in the Drinking Water Studies of Dibromoacetic Acid

Preparation
A premix solution was prepared by adding the appropriate amount of dibromoacetic acid and water to a flask and mixing with a stir bar until dibromoacetic acid was in solution. The premix was added to a partially filled mixing tank, the premix container rinsed (five times), and the rinsate added to the tank and mixed for up to 2 minutes. The tank was filled to the desired volume and mixed for up to 5 minutes. While mixing, the pH of the solution was adjusted to pH 5 by the addition of 1 N sodium hydroxide or hydrochloric acid as necessary, after which the formulation was mixed for at least 10 minutes.

Chemical Lot Number
46019/1 55196

Maximum Storage Time
42 days

Storage Conditions
Stored in Nalgene® containers at 5° C

Study Laboratory
Southern Research Institute (Birmingham, AL)

TABLE I2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Week Drinking Water Studies of Dibromoacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Rats and Mice				
November 13, 1998	November 16-18, 1998	125	137	+10
		250	267	+7
		500	504	+1
		1,000	972	–3
		2,000	2,038	+2
Animal Room Samples				
Rats				
November 13, 1998	December 1-2, 1998	125	129	+3
		250	247	–1
		500	522	+4
		1,000	1,035	+4
		2,000	2,068	+3
Mice				
November 13, 1998	December 3-5, 1998	125	119	–5
		125	130	+4
		125	112	–10
		125	118	–6
		250	261	+4
		250	246	–2
		500	532	+6
		500	507	+1
		500	470	–6
		500	479	–4
		1,000	1,066	+7
		1,000	964	–4
		1,000	1,008	+1
		1,000	912	–9
		2,000	1,900	–5
		2,000	1,953	–2
		2,000	2,003	+2
		2,000	2,075	+4

[a] Results of duplicate analyses

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Drinking Water Studies of Dibromoacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Rats and Mice				
February 10, 1999	February 11-12, 1999	125	119	–5
		250	248	–1
		500	489	–2
		1,000	973	–3
		2,000	1,841	–8
February 11, 1999	February 11-12, 1999	125	121	–3
		250	234	–6
		500	493	–1
		1,000	1,033	+3
		2,000	1,889	–6
March 10, 1999	March 11-12, 1999	125	141[b]	+12
		250	279[b]	+12
		500	546	+9
		1,000	1,059[b]	+6
		2,000	2,271[b]	+14
March 12, 1999	March 12-13, 1999	125	124[c]	–1
		250	249[c]	0
		2,000	1,897[c]	–5
May 5, 1999	May 5-8, 1999	125	120	–4
		250	243	–3
		500	491	–2
		1,000	967	–3
		2,000	1,935	–3
Animal Room Samples				
Rats				
February 10, 1999	March 16-18, 1999	125	106	–15
		250	243	–3
		500	480	–4
		1,000	947	–5
		2,000	1,877	–6
March 10, 1999	April 13-14, 1999	500	554	+11
		1,000	1,128	+13
March 12, 1999	April 13-14, 1999	125	136	+9
		250	280	+12
		2000	2,095	+5
May 5, 1999	May 19-20, 1999	125	129	+3
		250	247	–1
		500	488	–2
		1,000	1,060	+6
		2,000	1,993	0

TABLE I3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 3-Month Drinking Water Studies of Dibromoacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Animal Room Samples (continued)				
Mice				
February 10, 1999	March 16-18, 1999	125	118	–6
		250	240	–4
		500	485	–3
		1,000	989	–1
		2,000	2,009	0
March 10, 1999	April 13-14, 1999	500	516	+3
		1,000	921	–8
March 12, 1999	April 13-14, 1999	125	123	–2
		250	243	–3
		2000	1,889	–6
May 5, 1999	May 19-20, 1999	125	122	–2
		250	246	–1
		500	500	0
		1,000	999	0
		2,000	1999	0

[a] Results of duplicate analyses
[b] Not used in study
[c] Results of remix

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Dibromoacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Rats and Mice				
February 15, 2000	February 15-16, 2000	50	50	0
		500	514	+3
		1,000	1,009	+1
April 11, 2000	April 13-14, 2000	50	50	0
		500	486	–3
		1,000	981	–2
June 20, 2000	June 21-22, 2000	50	55[b]	+10
		500	551[b]	+10
		1,000	1,092	+9
June 26, 2000	June 27, 2000	500	507[c]	+1
August 29, 2000	August 30-31, 2000	50	50	0
		500	486	–3
		1,000	953	–5
November 7, 2000	November 8-9, 2000	50	49	–2
		500	493	–1
		1,000	1,016	+2
January 17, 2001	January 18-20, 2001	50	50	0
		500	499	0
		1,000	970	–3
March 27, 2001	March 28-29, 2001	50	48	–4
		500	494	–1
		1,000	982	–2
June 6, 2001	June 7-8, 2001	50	50	0
		500	505	+1
		1,000	1,030	+3
August 15, 2001	August 16, 2001	50	50	0
		500	503	+1
		1,000	976	–2
October 24, 2001	October 25-26, 2001	50	50	–1
		500	506	+1
		1,000	1,015	+2
January 2, 2002	January 4-8, 2002	50	50	0
		500	501	0
		1,000	1,024	+2

TABLE I4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Dibromoacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Animal Room Samples				
Rats				
February 15, 2000	March 27-28, 2000	50	52	+4
		500	507	+1
		1,000	1,027	+3
August 29, 2000	September 25-26, 2000	50	48	-4
		500	498	0
		1,000	985	–2
March 27, 2001	April 17-18, 2001	50	51	+2
		500	512	+2
		1,000	1,105	+11
October 24, 2001	November 19-20, 2001	50	49	–2
		500	503	+1
		1,000	991	–1
Mice				
February 15, 2000	March 27-28, 2000	50	51	+2
		500	499	0
		1,000	1,049	+5
August 29, 2000	September 25-26, 2000	50	49	–2
		500	488	–2
		1,000	998	0
March 27, 2001	April 17-18, 2001	50	52	+4
		500	549	+10
		1,000	1,082	+8
October 24, 2001	November 19-20, 2001	50	49	–2
		500	495	–1
		1,000	974	–3

[a] Results of duplicate analyses
[b] Not used
[c] Results of remix

APPENDIX J
WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF DIBROMOACETIC ACID

TABLE J1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

Week	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	15.8	108	16.4	110	8	16.7	110	76	17.1	108	158
2	18.0	140	17.9	143	6	17.9	145	62	18.8	142	132
3	18.6	174	18.2	173	5	18.2	179	51	18.7	178	106
4	18.4	203	18.1	205	4	18.2	206	44	18.2	206	88
5	19.2	227	18.9	227	4	18.3	229	40	18.3	230	80
6	18.6	254	18.3	253	4	18.2	255	36	18.2	255	71
7	18.7	271	18.3	268	3	17.8	268	33	17.9	272	66
8	18.3	286	17.9	283	3	17.0	283	30	17.4	285	61
9	18.1	303	18.8	296	3	17.8	296	30	17.0	299	57
10	18.2	319	17.7	314	3	17.2	311	28	16.8	313	54
11	17.3	325	17.3	319	3	16.5	314	26	16.4	316	52
12	17.0	337	17.2	329	3	16.2	323	25	15.7	325	48
13	16.8	350	17.4	338	3	16.3	330	25	16.0	331	48
17	17.6	374	17.6	368	2	16.4	360	23	16.7	357	47
21	15.8	398	16.1	392	2	15.4	382	20	15.3	377	41
25	16.7	418	17.3	413	2	17.0	401	21	16.0	398	40
29	16.3	434	16.5	430	2	16.0	416	19	15.6	413	38
33	15.9	452	15.6	445	2	14.8	432	17	15.0	427	35
37	15.6	467	15.3	458	2	15.2	442	17	14.4	438	33
41	16.4	473	16.2	467	2	15.9	452	18	15.4	445	35
45	15.9	484	15.8	475	2	15.6	462	17	14.8	452	33
49	16.4	494	16.7	484	2	15.7	468	17	15.2	457	33
53	15.3	503	15.4	491	2	15.3	475	16	14.6	462	32
57	18.7	509	18.9	498	2	18.0	483	19	16.9	467	36
61	16.7	516	17.0	501	2	16.0	485	17	14.5	467	31
65	15.4	519	15.3	501	2	14.9	485	15	13.9	462	30
69	15.7	522	15.2	507	2	14.8	489	15	13.9	467	30
73	16.3	523	15.5	504	2	15.2	491	16	14.0	469	30
77	16.1	522	16.5	508	2	16.6	486	17	14.0	462	30
81	16.1	522	16.8	509	2	15.2	487	16	14.0	457	31
85	17.1	512	17.7	506	2	16.8	474	18	15.0	449	33
89	18.3	516	18.7	503	2	18.0	479	19	16.0	441	36
93	17.5	521	17.1	492	2	15.9	477	17	14.3	450	32
97	16.7	515	16.8	496	2	16.3	463	18	15.0	445	34
101	18.1	509	18.7	504	2	17.1	457	19	14.9	435	34
Mean for weeks											
1-13	17.9	254	17.9	251	4	17.4	250	39	17.4	251	79
14-52	16.3	444	16.3	437	2	15.8	424	19	15.4	418	37
53-101	16.8	516	16.9	502	2	16.2	479	17	14.7	456	32

[a] Grams of water consumed per animal per day
[b] Milligrams of dibromoacetic acid consumed per kilogram body weight per day

TABLE J2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of Dibromoacetic Acid

Week	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	12.4	92	12.3	92	7	12.8	92	69	13.3	95	140
2	13.3	112	13.1	114	6	13.4	116	58	13.7	119	116
3	13.1	126	12.6	126	5	12.8	130	49	12.6	132	96
4	13.3	140	12.1	140	4	13.0	145	45	12.1	147	82
5	13.4	152	13.2	150	4	13.1	154	43	12.8	156	82
6	13.8	160	12.7	159	4	13.0	163	40	12.5	163	77
7	13.1	167	12.5	166	4	12.6	170	37	12.5	171	73
8	13.3	171	12.5	170	4	12.1	174	35	11.8	173	68
9	12.3	176	12.8	174	4	12.3	178	35	12.0	179	67
10	12.4	181	11.7	181	3	11.4	184	31	11.7	183	64
11	11.9	185	11.3	183	3	11.1	184	30	10.8	184	59
12	11.9	190	11.1	187	3	10.9	189	29	10.7	189	57
13	11.3	192	11.3	189	3	10.7	190	28	10.0	189	53
17	12.1	207	11.9	204	3	11.3	205	28	10.9	207	52
21	10.8	219	10.5	219	2	9.7	219	22	9.3	215	43
25	11.6	220	11.6	218	3	10.8	220	25	9.9	218	46
29	11.4	229	11.2	225	3	9.9	228	22	9.9	225	44
33	10.9	239	10.8	235	2	10.1	236	21	9.5	236	40
37	11.0	244	10.6	242	2	9.5	242	20	8.8	241	37
41	11.1	251	10.9	251	2	10.4	250	21	9.8	243	40
45	10.9	258	10.8	257	2	10.4	252	21	9.8	249	39
49	11.6	265	11.4	265	2	10.7	259	21	10.1	254	40
53	10.9	276	10.9	276	2	10.1	272	19	9.6	260	37
57	13.9	287	13.9	286	2	13.0	278	23	12.0	268	45
61	11.8	294	11.9	295	2	11.6	288	20	10.2	272	38
65	11.4	306	10.6	305	2	10.2	292	18	10.0	281	36
69	11.6	312	11.3	313	2	11.2	298	19	10.4	288	36
73	12.2	317	11.4	319	2	11.2	307	18	10.1	292	35
77	13.0	326	12.1	324	2	11.7	316	19	11.5	294	39
81	13.1	332	12.9	329	2	12.3	317	19	10.8	296	36
85	14.0	334	14.1	333	2	13.4	316	21	11.8	301	39
89	15.5	342	15.4	338	2	14.0	324	22	12.8	304	42
93	13.8	346	13.7	347	2	12.6	326	19	10.7	307	35
97	14.2	350	12.7	347	2	13.6	332	21	10.8	303	36
101	15.8	351	14.1	340	2	14.3	336	21	11.7	306	38
Mean for weeks											
1-13	12.7	157	12.2	156	4	12.2	159	41	12.0	160	80
14-52	11.3	237	11.1	235	2	10.3	235	22	9.8	232	42
53-101	13.2	321	12.7	319	2	12.3	308	20	11.0	290	38

[a] Grams of water consumed per animal per day
[b] Milligrams of dibromoacetic acid consumed per kilogram body weight per day

TABLE J3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	3.8	21.9	4.1	22.1	9	4.1	22.4	92	4.0	22.5	177
2	4.0	24.2	4.1	24.4	8	4.0	24.9	80	4.0	24.7	162
3	4.2	25.7	4.2	25.9	8	3.9	26.3	74	3.9	26.2	149
4	4.3	27.1	4.3	27.4	8	4.0	27.8	73	3.9	27.5	143
5	4.2	28.9	4.4	29.2	8	3.9	29.3	66	3.8	29.1	130
6	4.0	30.2	4.2	30.6	7	3.7	30.6	61	3.7	30.1	122
7	4.0	31.9	4.0	32.4	6	3.5	32.2	55	3.7	31.9	116
8	4.0	33.4	4.0	33.8	6	3.4	33.4	52	3.3	33.1	101
9	4.0	34.8	4.1	35.1	6	3.6	34.4	52	3.7	33.9	109
10	3.8	35.9	3.9	36.3	5	3.8	35.6	54	3.7	35.2	106
11	3.7	37.4	3.7	37.9	5	3.5	36.9	48	3.3	36.6	91
12	3.7	38.3	3.8	39.1	5	3.5	38.3	45	3.6	37.8	94
13	3.8	39.7	3.8	40.2	5	3.4	39.3	44	3.2	38.9	83
17	3.4	43.7	3.4	44.8	4	3.0	43.0	35	3.1	42.7	74
21	3.8	47.0	3.7	47.8	4	3.5	46.8	38	3.4	46.5	72
25	3.8	49.4	3.8	49.6	4	3.5	48.9	36	3.2	49.3	65
29	4.0	50.0	4.2	50.5	4	3.8	49.8	38	3.8	50.0	76
33	3.6	50.9	3.9	51.3	4	3.5	50.5	35	3.4	50.8	67
37	3.9	52.2	4.5	52.6	4	3.8	51.7	37	3.5	51.8	68
41	3.8	52.1	4.1	52.9	4	3.8	52.2	36	3.5	52.2	66
45	4.0	52.2	4.5	52.5	4	4.0	52.3	38	3.9	52.3	75
49	4.3	52.1	4.8	53.0	5	4.4	52.4	42	4.0	52.8	75
53	4.4	52.2	4.8	53.3	5	4.2	52.6	40	3.9	53.1	73
57	4.5	51.1	4.6	52.7	4	4.4	52.6	42	4.1	52.8	78
61	5.1	52.0	5.4	53.3	5	5.2	53.1	49	5.1	53.1	95
65	4.6	52.5	4.9	54.0	5	4.6	53.4	43	4.3	53.8	80
69	4.3	51.7	4.5	54.0	4	4.5	53.3	42	4.0	52.6	77
73	4.3	52.1	4.6	54.1	4	4.4	53.0	41	4.3	52.6	81
77	4.6	51.6	4.6	53.8	4	4.6	52.9	44	4.5	52.0	86
81	4.7	51.8	4.8	53.8	5	4.7	52.1	45	4.6	52.0	89
85	4.8	50.7	4.9	52.8	5	5.0	51.9	49	4.8	50.5	95
89	4.6	48.7	4.5	51.7	4	5.0	51.5	48	4.9	50.3	97
93	4.2	48.1	4.5	51.0	4	5.0	51.6	48	5.0	49.3	101
97	4.1	47.3	4.2	49.9	4	4.9	50.5	49	4.7	48.3	98
101	4.4	46.7	4.7	50.0	5	5.6	51.1	54	5.3	46.6	114
Mean for weeks											
1-13	4.0	31.5	4.0	31.9	7	3.7	31.7	61	3.7	31.3	122
14-52	3.9	49.9	4.1	50.6	4	3.7	49.8	37	3.5	49.8	71
53-101	4.5	50.5	4.7	52.6	5	4.8	52.3	46	4.6	51.3	90

[a] Grams of water consumed per animal per day
[b] Milligrams of dibromoacetic acid consumed per kilogram body weight per day

TABLE J4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Dibromoacetic Acid

	0 mg/L		50 mg/L			500 mg/L			1,000 mg/L		
Week	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	3.1	18.4	3.3	18.6	9	3.2	18.8	85	3.0	18.5	164
2	3.4	19.4	4.1	19.3	11	3.3	19.7	84	3.2	19.7	163
3	3.7	20.5	4.2	20.4	10	3.9	20.8	93	3.5	20.7	169
4	3.5	21.2	3.8	21.1	9	3.9	21.5	90	3.4	21.3	161
5	4.0	22.2	4.0	22.2	9	3.6	22.7	80	3.2	22.5	141
6	3.9	23.4	4.3	23.3	9	3.5	23.9	72	3.4	23.5	144
7	3.7	24.3	3.4	24.2	7	3.5	24.7	72	3.3	24.4	137
8	3.6	24.6	3.6	24.9	7	3.4	25.4	68	3.2	24.9	131
9	3.6	25.7	3.6	25.7	7	3.7	26.3	71	3.6	25.8	138
10	3.9	26.7	4.0	26.1	8	3.3	27.4	61	3.3	26.7	125
11	3.5	28.0	3.5	27.8	6	3.3	28.3	59	3.1	27.8	112
12	3.8	28.4	4.1	28.3	7	3.3	29.4	56	3.3	27.9	117
13	4.0	29.8	4.0	29.0	7	3.5	30.0	59	2.8	29.2	96
17	3.2	34.8	3.2	34.0	5	3.0	34.7	44	2.9	33.0	87
21	4.6	38.9	3.5	38.2	5	3.3	38.4	43	3.0	36.3	81
25	3.9	44.0	3.2	44.0	4	3.3	43.5	38	2.7	42.1	64
29	3.5	47.6	3.0	47.9	3	2.7	46.7	29	2.6	45.0	58
33	3.0	49.7	2.4	50.4	2	3.4	49.2	35	3.1	47.1	66
37	2.5	53.5	2.6	54.6	2	2.7	52.4	26	2.6	50.4	51
41	2.6	56.2	2.8	56.2	3	2.8	54.3	26	2.6	52.4	49
45	2.9	57.0	2.8	57.9	2	2.7	55.5	25	3.0	53.9	56
49	3.4	58.0	2.7	59.1	2	2.8	57.3	25	2.7	55.6	48
53	2.8	60.1	3.2	60.4	3	2.7	59.2	23	2.6	57.3	45
57	2.6	60.9	2.8	60.6	2	2.9	59.8	24	2.8	58.2	48
61	3.3	63.4	3.5	62.1	3	3.5	61.2	29	3.3	60.0	55
65	3.1	63.5	2.8	62.3	2	2.7	62.0	22	2.5	61.0	41
69	2.5	64.1	2.7	62.7	2	2.7	62.5	21	2.4	61.2	39
73	2.6	63.8	3.0	63.1	2	2.9	62.9	23	2.7	61.1	44
77	2.7	64.3	2.9	63.6	2	3.1	63.3	24	2.6	62.0	41
81	2.9	63.2	3.2	63.1	3	3.3	61.3	27	2.7	60.7	44
85	3.0	63.1	3.0	61.8	3	3.1	61.8	25	2.9	59.2	49
89	3.2	63.2	3.2	62.5	3	3.4	61.4	27	2.8	60.4	46
93	3.2	63.6	3.2	63.9	3	3.9	61.9	32	3.3	60.9	54
97	3.1	60.8	3.0	62.1	2	3.8	59.2	32	3.3	58.3	57
101	4.0	59.0	3.3	59.5	3	4.0	57.9	35	3.8	56.6	67
Mean for weeks											
1-13	3.7	24.0	3.8	23.9	8	3.5	24.5	73	3.3	24.1	138
14-52	3.3	48.9	2.9	49.1	3	3.0	48.0	32	2.8	46.2	62
53-101	3.0	62.5	3.1	62.1	3	3.2	61.1	27	2.9	59.8	48

[a] Grams of water consumed per animal per day
[b] Milligrams of dibromoacetic acid consumed per kilogram body weight per day

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE K1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE K2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kilogram of finished product

TABLE K3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.1 ± 0.67	13.2 – 15.7	23
Crude fat (% by weight)	8.1 ± 0.29	7.6 – 8.6	23
Crude fiber (% by weight)	9.1 ± 0.58	8.0 – 10.5	23
Ash (% by weight)	5.2 ± 0.27	4.8 – 5.8	23
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	4,705 ± 799	3,060 – 6,810	23
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	7.1 ± 0.86	6.0 – 8.8	23
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	1.039 ± 0.047	0.964 – 1.140	23
Phosphorus (%)	0.606 ± 0.037	0.552 – 0.701	23
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE K4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.21 ± 0.023	0.16 – 0.25	23
Cadmium (ppm)	0.04 ± 0.005	0.04 – 0.06	23
Lead (ppm)	0.09 ± 0.099	0.05 – 0.54	23
Mercury (ppm)	< 0.02		23
Selenium (ppm)	0.23 ± 0.057	0.14 – 0.36	23
Aflatoxins (ppb)	< 5.00		23
Nitrate nitrogen (ppm)[c]	11.7 ± 3.52	6.85 – 21.1	23
Nitrite nitrogen (ppm)[c]	< 0.61		23
BHA (ppm)[d]	< 1.0		23
BHT (ppm)[d]	< 1.0		23
Aerobic plate count (CFU/gm)	14 ± 14	10 – 70	23
Coliform (MPN/gm)	2.8 ± 1.3	0.0 – 3.6	23
Escherichia coli (MPN/gm)	< 10		23
Salmonella (MPN/gm)	Negative		23
Total nitrosoamines (ppb)[e]	4.7 ± 1.19	3.1 – 7.5	23
N-Nitrosodimethylamine (ppb)[e]	2.1 ± 0.57	1.0 – 3.2	23
N-Nitrosopyrrolidine (ppb)[e]	2.6 ± 1.13	1.0 – 5.1	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.153 ± 0.095	0.020 – 0.418	23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.179 ± 0.143	0.020 – 0.557	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfane sulfate	<0.03		23

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 3-month and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to BioReliance Corporation (Rockville, MD) for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
3-Month Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Immunofluorescence Assay	
Parvovirus	Study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination
M. arthritidis	Study termination

Method and Test	Time of Analysis
MICE	
3-Month Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV (mouse hepatitis virus)	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
MCMV (mouse cytomegalovirus)	Study termination
Parvovirus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
EDIM	12 months, study termination
GDVII	Study termination
LCM	12 and 18 months
Mouse adenoma virus-FL	6 and 18 months
MCMV	Study termination
MHV	Study termination
PVM	12 months
Parvovirus	6, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX M
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

INTRODUCTION

A physiologically based pharmacokinetic (PBPK) model was developed to describe the uptake, distribution, and metabolism of dibromoacetic acid in female F344/N rats and male B6C3F$_1$ mice. This PBPK model was based on a published model for dichloroacetic acid (Keys *et al.*, 2004). A key feature of the dichloroacetic acid model is the inclusion of suicide inhibition in the description of dichloroacetic acid metabolism. Parameters fit to data in the dichloroacetic acid model that may be different for dibromoacetic acid were estimated by fitting model predictions to data from concurrent single-dose NTP toxicokinetic studies.

MODEL DEVELOPMENT

All features of Keys' model for dichloroacetic acid were retained for the current dibromoacetic acid model. The dibromoacetic acid model (Figure M1) has four flow-limited tissue compartments: liver, kidney, slowly perfused tissue, and rapidly perfused tissue. Keys *et al.* (2004) had an interest in modeling dichloroacetic acid that had been metabolically derived from intravenously administered trichloroethylene, and they provided no description of oral absorption kinetics. When these authors modeled drinking water studies, they assumed that 100 percent of the dose reached the liver instantaneously. Evaluation of Keys' model with dichloroacetic acid gavage data suggested that inclusion of oral absorption kinetics would be necessary for gavage study simulation. A stomach compartment was added with a linear uptake rate to the liver.

Urinary elimination was modeled using published values for urine flow to describe the rate of removal of dibromoacetic acid from the kidney tubule region. Published values for glomerular filtration were used to describe the distribution of dibromoacetic acid into kidney tissue and tubule regions (Davies and Morris, 1993). There was also saturable reabsorption from the kidney tubule region into kidney tissue. Keys' model includes glutathione-*S*-transferase$_{zeta}$-mediated metabolism with suicide inhibition as well as a linear, non-glutathione-*S*-transferase$_{zeta}$-mediated pathway. For dichloroacetic acid, the glutathione-*S*-transferase$_{zeta}$ pathway leads to glyoxylate, while the metabolite resulting from the second pathway has not been determined (Keys *et al.*, 2004). The dibromoacetic acid model includes both pathways.

The physiological parameters in Table M1 were taken from Brown *et al.* (1997). Due to similarities of structure, behavior, and octanol:water partition coefficients for the haloacetates, the partition coefficients for dibromoacetic acid (Table M2) were those provided for dichloroacetic acid in Keys' model.

The NTP toxicokinetic data used for parameter estimation included blood concentrations of dibromoacetic acid and urine content of dibromoacetic acid and its metabolites glyoxylic acid and oxalic acid. In these studies, blood and urine samples were collected from female F344/N rats administered single intravenous injections of 10 or 110 mg dibromoacetic acid/kg body weight or single gavage doses of 10, 40, or 100 mg/kg; similar samples were collected from male B6C3F$_1$ mice administered single intravenous injections of 100 mg/kg or single gavage doses of 100, 200, or 400 mg/kg. For rats and mice, samples were collected from three animals per timepoint for blood concentration analysis and from three groups of three animals each for urine concentration analysis.

There were seven unknown parameters in the model that had very little information to suggest the correct order of magnitude. Therefore, the values of the parameters were first found using a differential evolution optimization algorithm (ICSI, 1995). This type of algorithm has the ability to search across the global parameter space without being restricted to a local minimum. A cost function computed the sum of squared errors between the simulated results and experimental measurements for blood and urine. Another cost function computed the natural logarithm of the sum of squared errors, but the results from both cost functions were similar. The differential evolution algorithm was run for at least 200 generations. The best parameters from the differential evolution algorithm were then used as the initial conditions in the constrained optimization routine in MATLAB® (The Math Works, Inc., Natick, MA) to find the final parameter values (Table M3).

Definitions of Abbreviations

A_i = Amount in tissue compartment *i* (mg)
V_i = Volume of tissue compartment *i* (L)
C_i = Concentration in tissue compartment *i* (mg/L)
$C_{v,i}$ = Concentration in venous blood of tissue compartment *i* (mg/L)
Q_i = Blood flow rate for tissue compartment *i*; if *i=urine*, then urine flow rate (L/hour)
P_i = Tissue compartment *i*: blood partition coefficient
k_{abs} = Linear rate of absorption from stomach ($hour^{-1}$)
V_{max} = Maximum metabolism rate (mg/hour)
K_m = Michaelis-Menten constant associated with metabolism (mg/L)
k_f = Linear rate of metabolism ($hour^{-1}$)
k_d = Inhibition constant ($hour^{-1}$)
k_s = Rate of resynthesis ($mg/hour^2$)
k_{de} = Degradation rate ($hour^{-1}$)
GFR = Glomerular filtration rate (L/hour)
T_{max} = Maximum reabsorption rate (mg/hour)
K_t = Michaelis-Menten constant associated with tubular reabsorption (mg/L)

Model Equations

Amount in stomach compartment:

$$\frac{dA_{stomach}}{dt} = dose_{oral} + dose_{drink} - k_{abs} A_{stomach}$$

Amount in rapidly/slowly perfused tissue compartments:

$$\frac{dA_{tissue}}{dt} = Q_{tissue}\left(C_{arterial} - C_{v,tissue}\right)$$

Rate of metabolism:

$$\frac{dA_m}{dt} = \frac{V_{max} C_{v,l}}{K_m + C_{v,l}} + k_f A_l$$

Change in maximum rate of glutathione-*S*-transferase$_{zeta}$ metabolism:

$$\frac{dV_{max}}{dt} = -k_d \frac{V_{max} C_{v,l}}{K_m + C_{v,l}} + k_s - k_{de} V_{max} : V_{max}(0) = V_{max0}$$

Amount in liver tissue compartment:

$$\frac{dA_l}{dt} = Q_l\left(C_{arterial} - C_{v,l}\right) + \frac{dA_{stomach}}{dt}$$

Amount in kidney tubule compartment:

$$\frac{dA_{kidTub}}{dt} = GFR \cdot C_{v,k} - \frac{C_{kidTub} T_{max}}{C_{kidTub} + K_t} - \frac{dA_{urine}}{dt}$$

Amount in kidney tissue compartment:

$$\frac{dA_k}{dt} = Q_k\left(C_{arterial} - C_{v,k}\right) + \frac{C_{kidTub}T_{max}}{C_{kidTub} + K_t} - GFR \cdot C_{v,k}$$

Amount eliminated through urine:

$$\frac{dA_{urine}}{dt} = Q_{urine}C_{kidTub}$$

Concentration in tissue compartment *i*:

$$C_i = \frac{A_i}{V_i}$$

Concentration in venous blood of tissue compartment *i*:

$$C_{v,i} = \frac{C_i}{P_i}$$

Resynthesis rate:

$$k_s = k_{de} \cdot V_{max0}$$

RESULTS

Figures M2 through M10 show the results of simulations performed with the PBPK model for dibromoacetic acid compared to the experimental data from the NTP toxicokinetic studies. Each figure represents one study and shows separate plots for blood concentration, urinary elimination, and the response of V_{max} over 48 hours. PBPK model predictions for blood concentrations of dibromoacetic acid and V_{max} during 2-week drinking water studies in rodents exposed to 50, 500, or 1,000 mg/L are shown in Figures M11 (F344/N rats) and M12 ($B6C3F_1$ mice).

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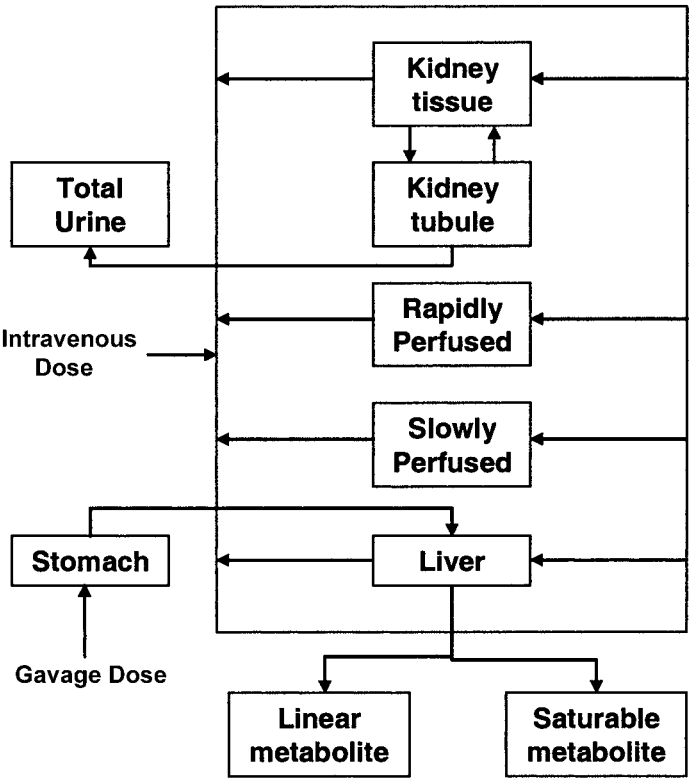

FIGURE M1
Physiologically Based Pharmacokinetic Model for F344/N Rats and B6C3F$_1$ Mice Exposed to Dibromoacetic Acid by Single-Dose Intravenous Injection or Oral Gavage

TABLE M1
Physiological Parameters for F344/N Rats and B6C3F$_1$ Mice for the Physiologically Based Pharmacokinetic Model of Dibromoacetic Acid[a]

	Female F344/N Rats	Male B6C3F$_1$ Mice
Parameter		
Body weight (kg)	0.1798	0.02782
Cardiac output (L/hour per kg$^{0.75}$ body weight)	14.1	16.5
Urine flow (L/hour per kg body weight)[b]	0.00833	0.00208
Glomerular filtration (L/hour per kg body weight)[b]	0.3144	0.84
Tissue Volume as Fraction of Body Weight		
Kidney tissue	0.0073	0.0167
Kidney tubule	0.000073	0.000167
Liver	0.0366	0.0549
Rapidly perfused tissue	0.1561	0.1283
Slowly perfused tissue	0.62	0.62
Tissue Blood Flow as Fraction of Cardiac Output		
Kidney	0.141	0.091
Liver	0.183	0.161
Rapidly perfused tissue	0.266	0.338
Slowly perfused tissue	0.41	0.41

[a] Except as noted, parameter estimates were determined from Brown *et al.* (1997).
[b] Parameter estimate was taken from Davies and Morris (1993).

TABLE M2
Partition Coefficients for Dibromoacetic Acid for the Physiologically Based Pharmacokinetic Model of Dibromoacetic Acid[a]

Tissue	Partition Coefficient
Kidney	0.14
Liver	1.08
Rapidly perfused tissue	1.08
Slowly perfused tissue	0.37

[a] All coefficients are expressed as tissue:blood ratios and are the same as those provided for dichloroacetic acid by Keys *et al.* (2004).

TABLE M3
Parameter Estimates for F344/N Rats and B6C3F$_1$ Mice from the Physiogically Based Pharmacokinetic Model of Dibromoacetic Acid

	Female F344/N Rats	Male B6C3F$_1$ Mice
k_{abs} (hour^{-1})	2.8766	2.0472
V_{max0c} (mg/hour per kg$^{0.75}$ body weight)	74.3186	133.6532
K_m (mg/L)	15.0064	33.7813
k_{fc} (hour^{-1}/kg$^{-0.25}$ body weight)	0.2910	0.0280
k_d (hour^{-1})	1.3166	0.2265
k_{de} (hour^{-1})	0.00875[a]	0.00875[a]
T_{max} (mg/hour)	28.5329	61.4492
K_t (mg/L)	61.5938	272.9621

[a] Value taken from Anderson *et al.* (1999).

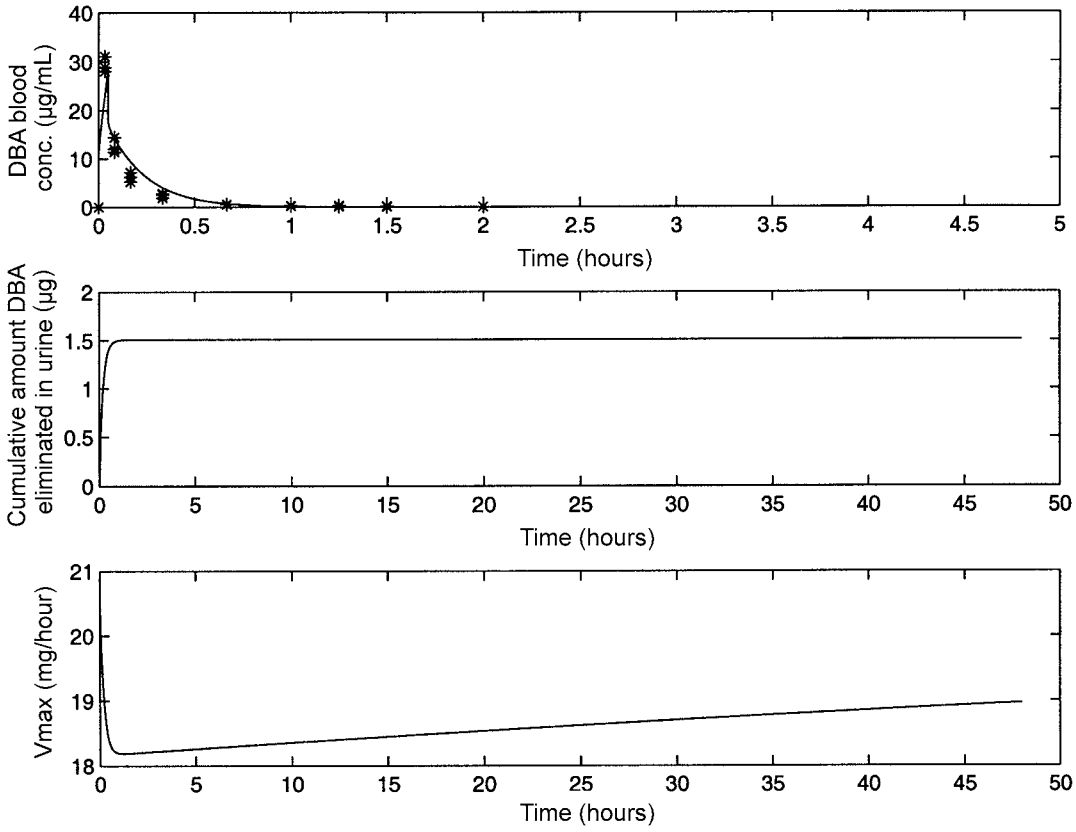

FIGURE M2
Data (Stars) and PBPK Model Predictions (Lines) for Female F344/N Rats Administered a Single Intravenous Injection of 10 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

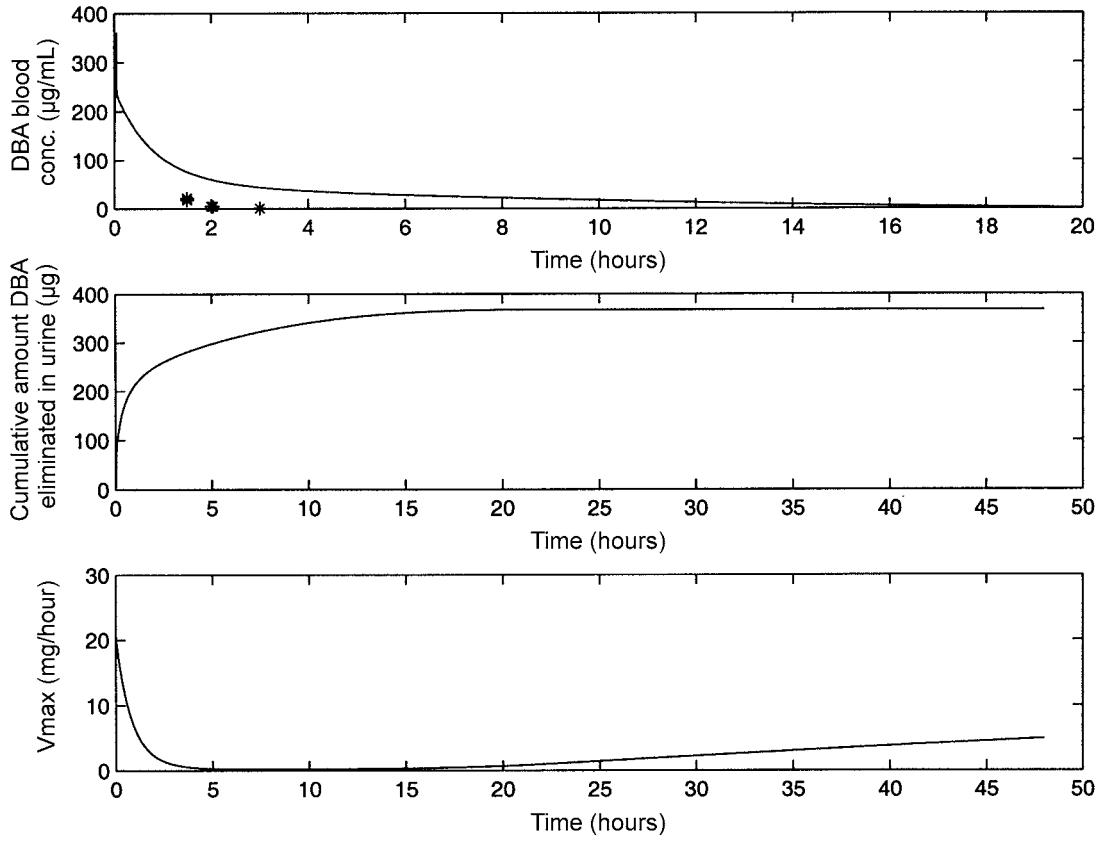

FIGURE M3
Data (Stars) and PBPK Model Predictions (Lines) for Female F344/N Rats Administered a Single Intravenous Injection of 110 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

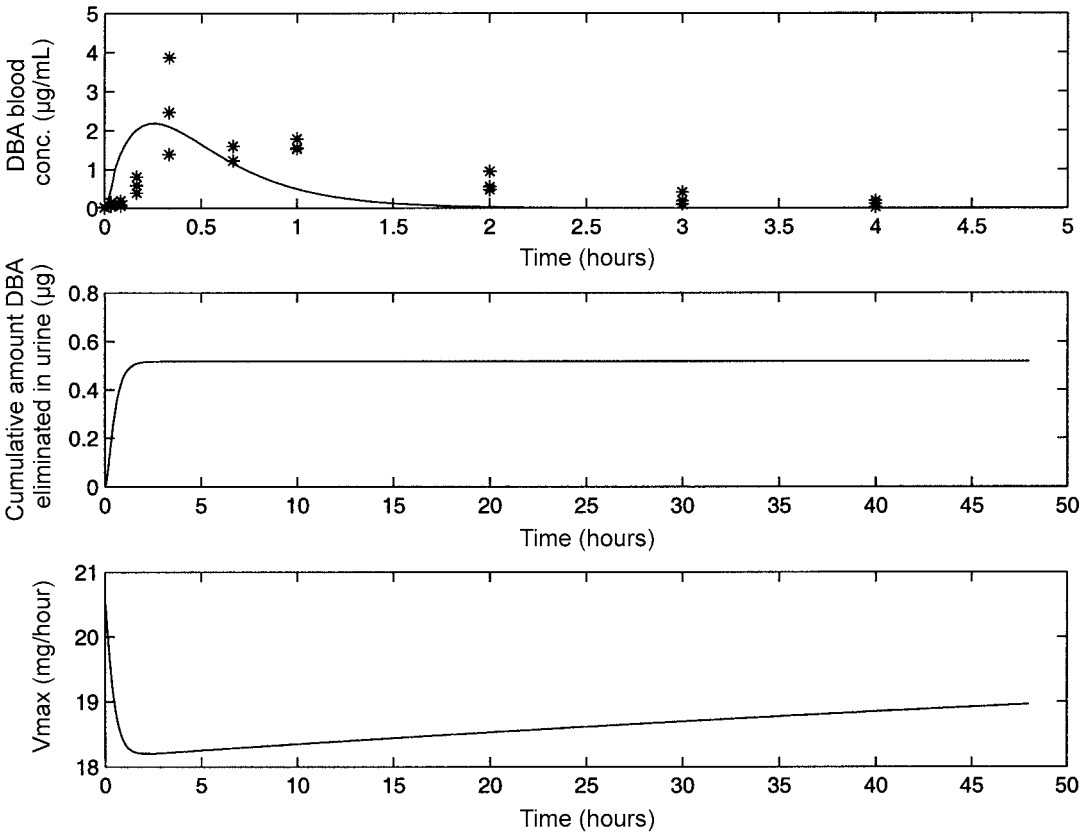

FIGURE M4
Data (Stars) and PBPK Model Predictions (Lines) for Female F344/N Rats Administered a Single Gavage Dose of 10 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

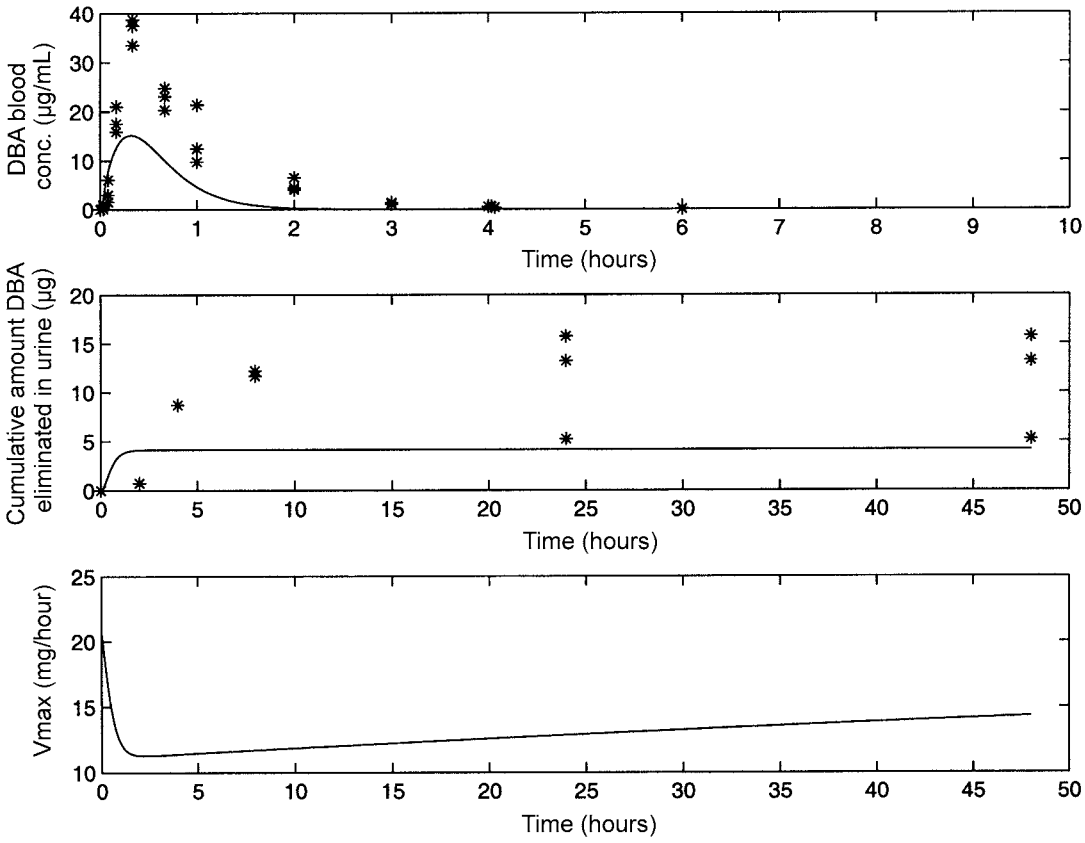

FIGURE M5
Data (Stars) and PBPK Model Predictions (Lines) for Female F344/N Rats Administered a Single Gavage Dose of 40 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

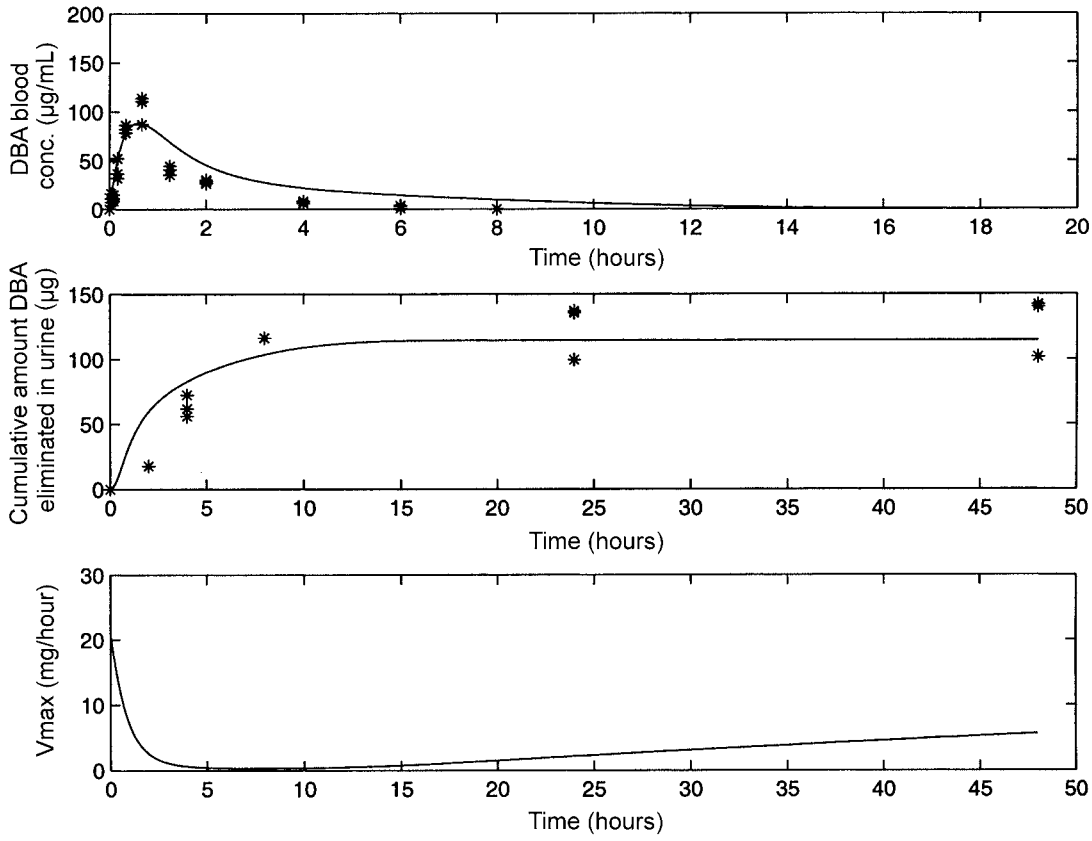

FIGURE M6
Data (Stars) and PBPK Model Predictions (Lines) for Female F344/N Rats Administered a Single Gavage Dose of 100 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

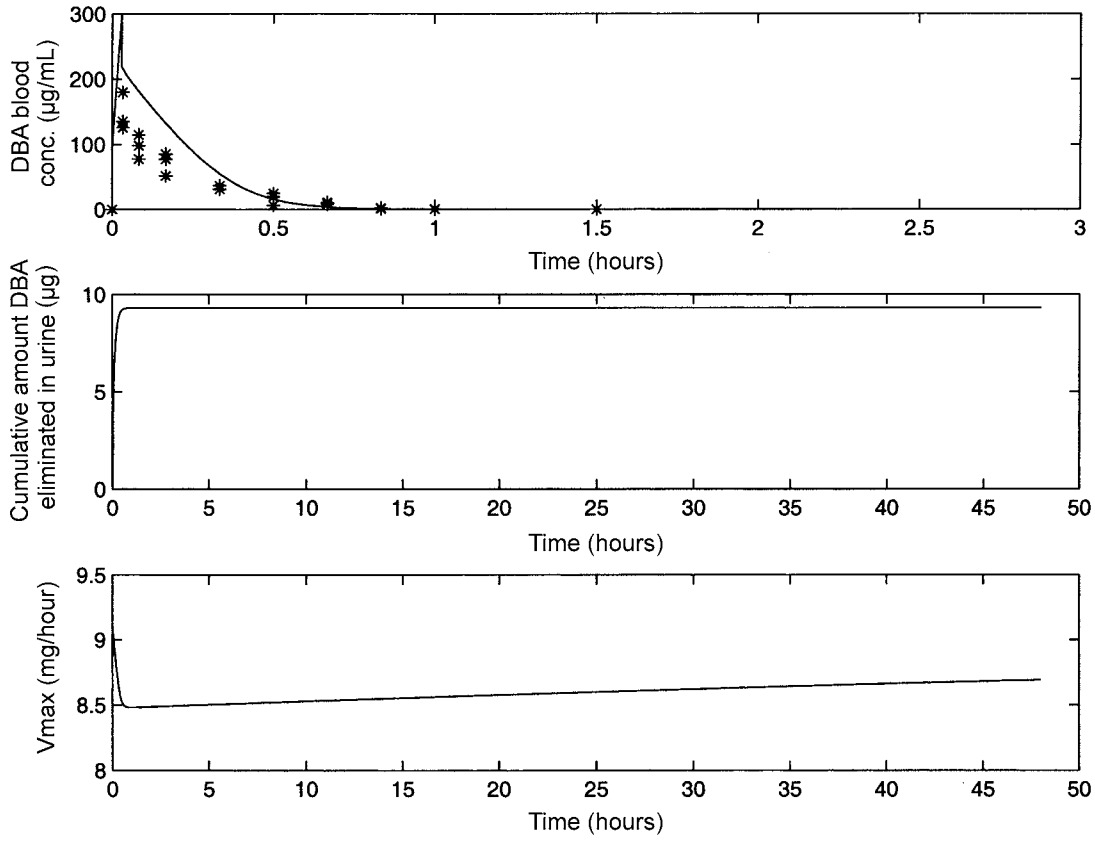

FIGURE M7
Data (Stars) and PBPK Model Predictions (Lines) for Male B6C3F$_1$ Mice Administered a Single Intravenous Injection of 100 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

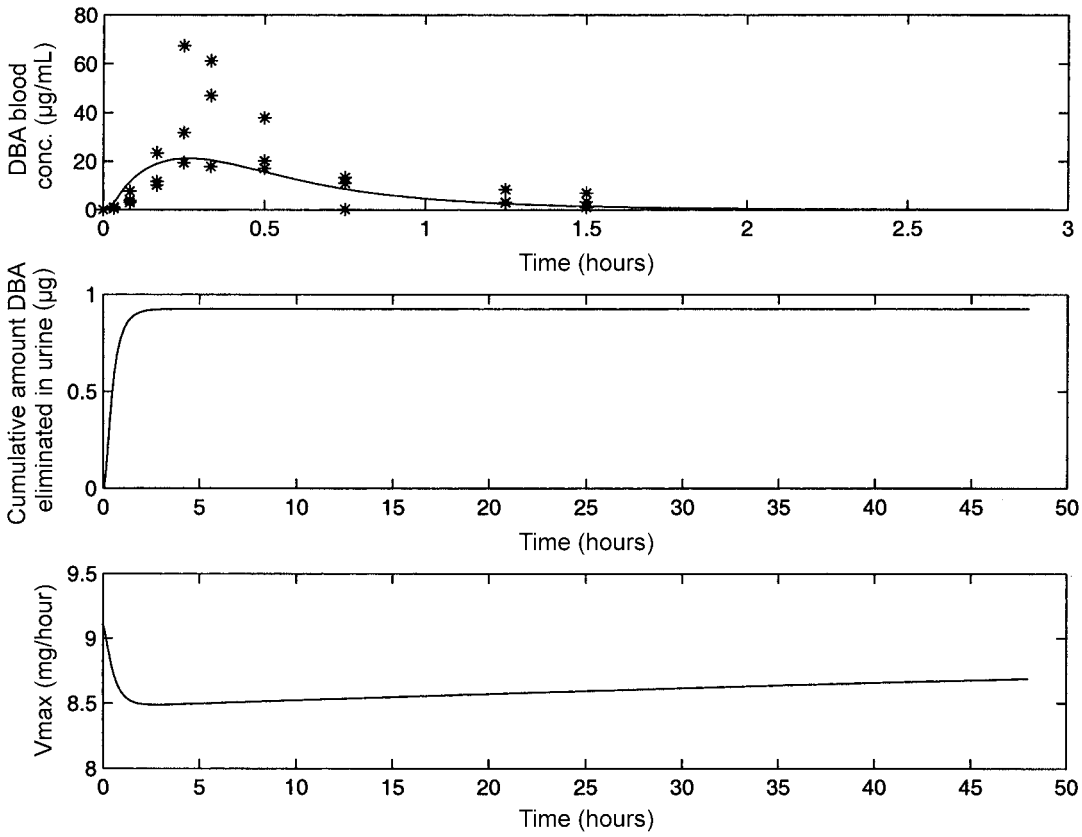

FIGURE M8
Data (Stars) and PBPK Model Predictions (Lines) for Male B6C3F$_1$ Mice Administered a Single Gavage Dose of 100 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

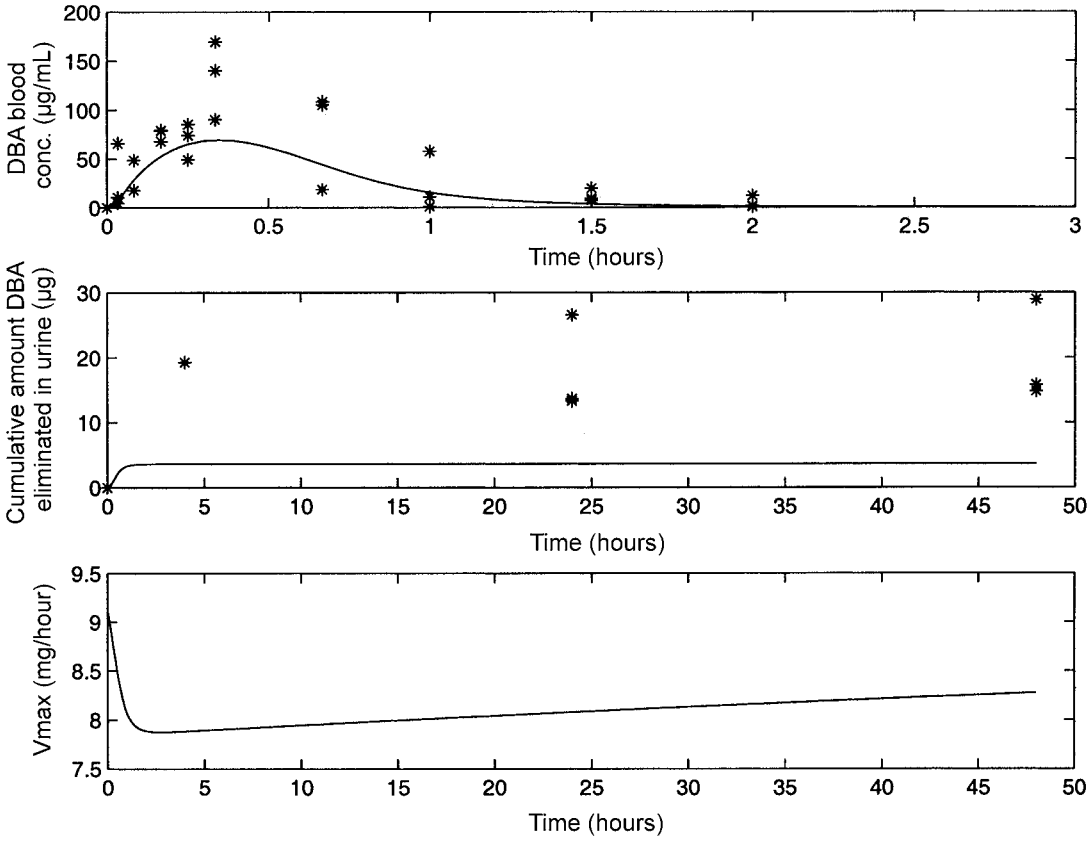

FIGURE M9
Data (Stars) and PBPK Model Predictions (Lines) for Male B6C3F$_1$ Mice Administered a Single Gavage Dose of 200 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

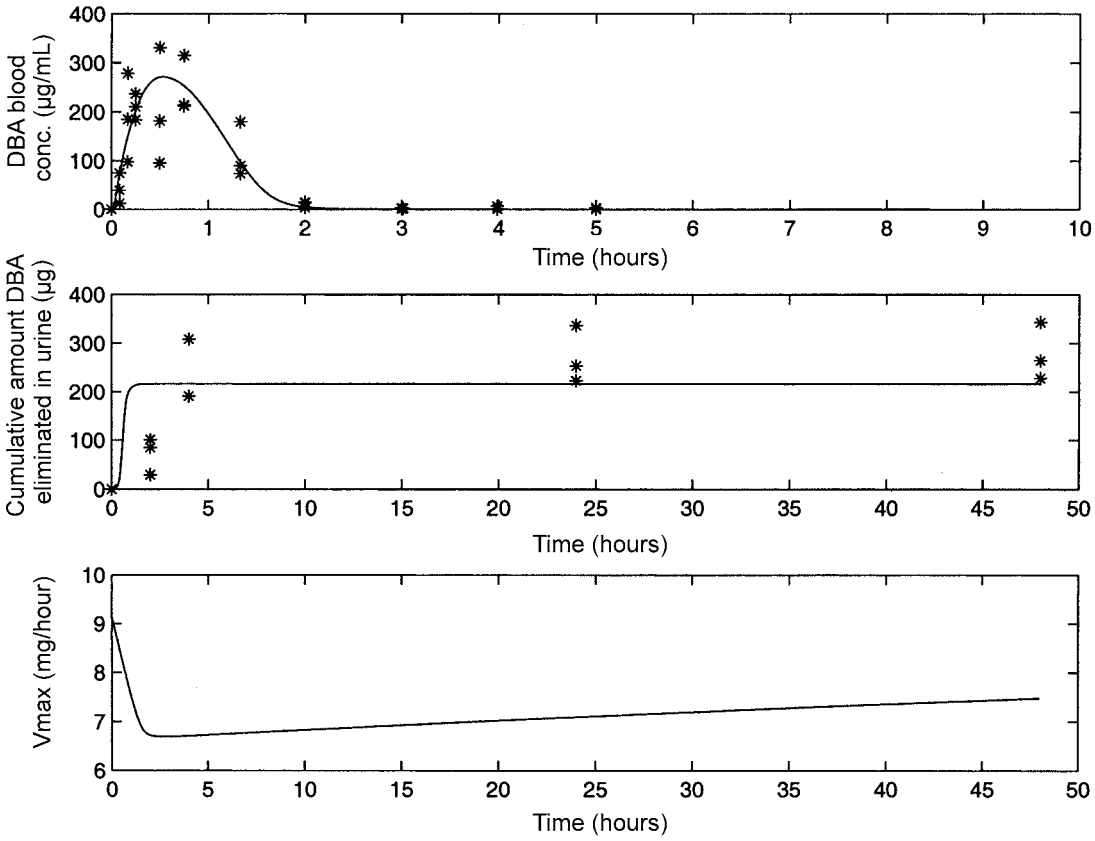

FIGURE M10
Data (Stars) and PBPK Model Predictions (Lines) for Male B6C3F$_1$ Mice Administered a Single Gavage Dose of 400 mg/kg Dibromoacetic Acid
Data are presented as the mean of three samples per timepoint.

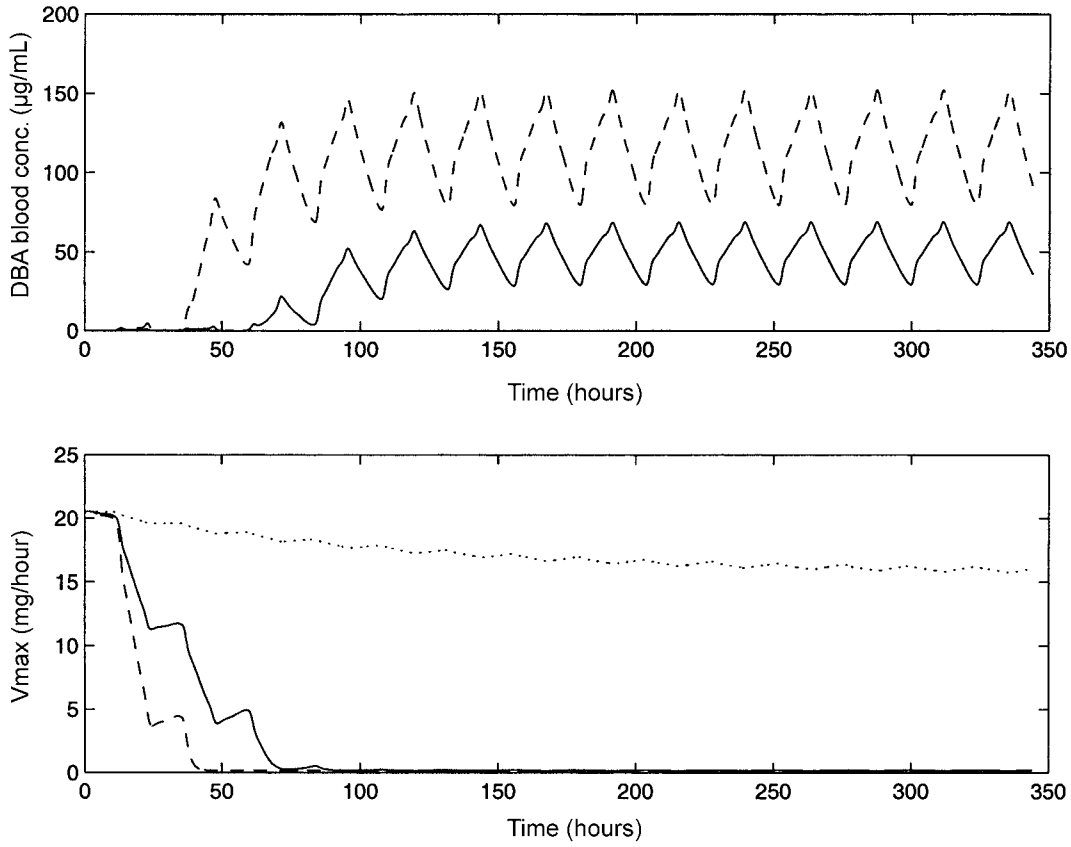

FIGURE M11
PBPK Model Predictions for Female F344/N Rats Administered 50 (Dotted Line), 500 (Solid Lines), or 1,000 (Dashed Lines) mg/L Dibromoacetic Acid in Drinking Water for 2 Weeks

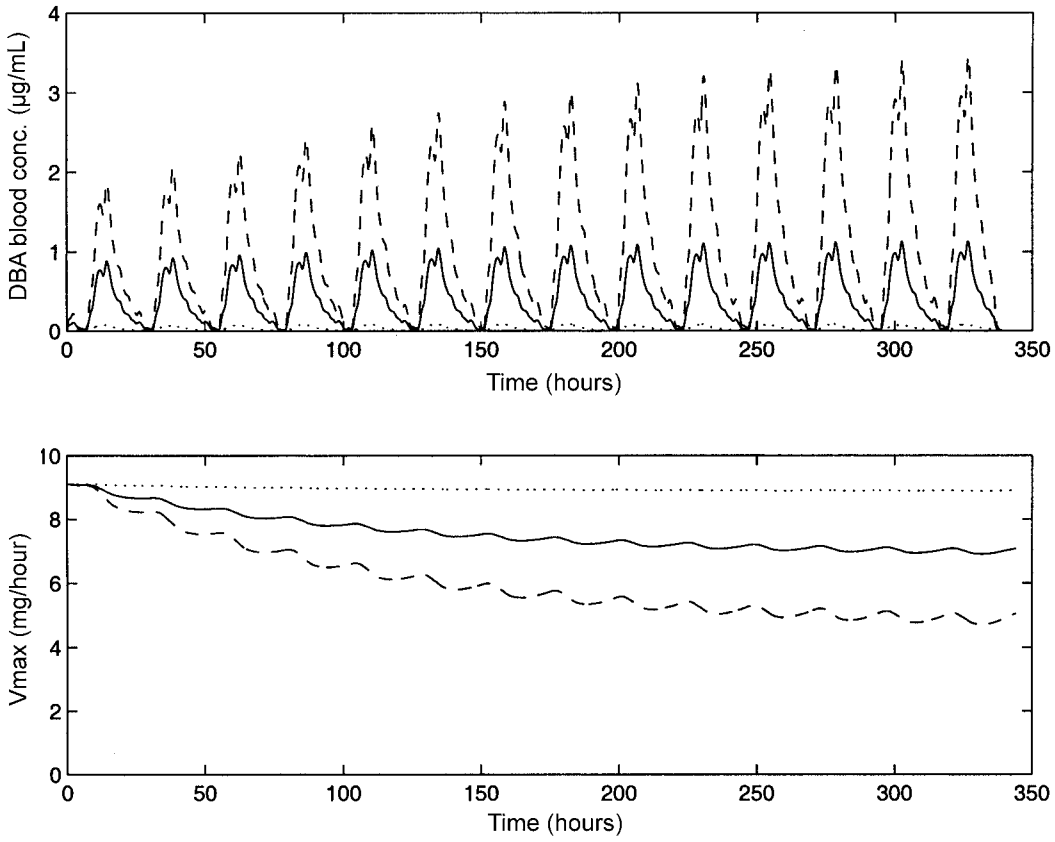

FIGURE M12
PBPK Model Predictions for Male B6C3F$_1$ Mice Administered 50 (Dotted Lines), 500 (Solid Lines), or 1,000 (Dashed Lines) mg/L Dibromoacetic Acid in Drinking Water for 2 Weeks

APPENDIX N
SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

SINGLE-DOSE TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

INTRODUCTION

Single-dose intravenous injection and gavage toxicokinetic studies were designed to estimate toxicokinetic parameters for the elimination of dibromoacetic acid from the plasma of F344/N rats and B6C3F$_1$ mice. Male and female F344/N rats received a single intravenous injection of 25 mg dibromoacetic acid/kg body weight or a single gavage dose of 25, 50, or 125 mg/kg. Male and female B6C3F$_1$ mice received a single intravenous injection of 70 mg/kg or a single gavage dose of 70, 175, or 350 mg/kg. Postdosing plasma samples were analyzed for dibromoacetic acid, and the results were used to calculate toxicokinetic parameters.

MATERIALS AND METHODS

Dibromoacetic acid (lot 46019/1 55196) was obtained from Fluka Chemie AG (Buchs, Switzerland), homogenized, repackaged in the original bottles, and stored at room temperature. The material was analyzed for identity and purity; the results and analytical systems are described in Appendix I.

On the day of dosing, the animals were 14 to 15 weeks old. For the gavage studies, male and female F344/N rats ranged in weight from 256.4 to 333.1 and 129.4 to 201.2 grams, respectively, and male and female B6C3F$_1$ mice ranged in weight from 21.0 to 35.1 and 14.0 to 29.4 grams, respectively. All doses of dibromoacetic acid were formulated in normal saline.

After dosing, animals were anesthetized with CO_2/O_2 prior to bleeding. Blood samples were collected using the retroorbital puncture method for rats and cardiac puncture for mice. Three rats and three mice were bled at each timepoint. Only one sample was collected from each mouse, but rats were bled twice with at least one hour between sample collections. Blood samples of approximately 1 mL (rats) and the maximum volume obtainable for mice (approximately 0.4 to 1 mL) were placed into individual tubes containing EDTA as an anticoagulant. Whole blood samples were gently rocked by hand to ensure adequate mixing with the anticoagulant and then placed on wet ice. Approximately 60 minutes after collection, the whole blood was centrifuged, and the plasma was transferred to a plastic storage vial. The plasma was stored at –70° C until analyzed.

For analysis, plasma samples were thawed to room temperature. Aliquots of 200 µL of plasma were combined with 50 µL of working internal standard solution (40 µg dichloroacetic acid/mL) and 500 µL of 12% boron trifluoride-methanol complex; the mixture was sealed and heated at approximately 115° C for 45 minutes. Two mL of dichloromethane and 1 mL of deionized water were added, and then the mixture was tumbled for 30 minutes and centrifuged at 1,500 rpm for 5 minutes. The lower (dichloromethane) layer was transferred to autosampler vials, and the vials were sealed. Chromatography was performed on a gas chromatography system (Agilent, Palo Alto, CA) equipped with an electron capture detector and an RTX-5 column (30 m × 0.53 mm ID, 1.5-µm film; Supelco, Inc., Bellefonte, PA). The temperature program was 50° C for 1 minute, increased to 150° C at 12° C/minute, and then increased to 300° C at 70° C/minute. Sample concentrations of dibromoacetic acid were calculated using 1/y-weighted quadratic regression analysis of instrument response to calibration standards prepared in blank F344/N rat plasma.

The analytical method for determining derivatized dibromoacetic acid in plasma samples was validated within a range of 0.1 to 2 µg/mL (low range) and 2 to 100 µg/mL (high range). The limit of quantitation was 0.1 µg/mL. Precision, based on standard deviation of quality control samples, was less than or equal to 15%. Accuracy, based on percent relative errors in the determined versus the prepared concentration of calibration standards, was less than or equal to 15% except at the limit of quantitation, where less than or equal to 20% was acceptable.

Toxicokinetics

Dibromoacetic acid plasma concentration versus time data were evaluated using WinNONLIN® (version 2.1; Scientific Consulting, Inc., Freeman, SD). A one-compartment model with no lag time and first-order absorption and elimination was used to fit the data:

$$C(t)=D \bullet K_{01} / V / (K_{01} - K_{10}) \bullet [\exp(K_{10} \bullet t) - \exp(K_{01} \bullet t)]$$

In this model, C(t) is the plasma concentration at time t, D is dose, V is volume of distribution, K_{01} is the absorption rate constant, and K_{10} is the elimination rate constant. These parameters were estimated by nonlinear regression using a least-squares method and a weighting factor ($1/y^2$ predicted).

AUC (area under the plasma concentration versus time curve) values were calculated using the trapezoidal rule:

$$AUC_t = \Sigma [(C_{n-1} + C_n) / 2 \times (t_n - t_{n-1})]$$

AUC extrapolated to infinity was calculated as:

$$AUC_{infinity} = AUC_t + (C_f / K_{10})$$

Clearance was calculated as $D/AUC_{infinity}$ and the half-lives for the absorption and elimination phases were calculated as $0.693/K_{01}$ and $0.693/K_{10}$, respectively.

Results and Discussion

Dibromoacetic acid was rapidly absorbed when administered by gavage in an aqueous formulation to male and female F344/N rats and $B6C3F_1$ mice such that measurable concentrations of dibromoacetic acid were observed within 5 minutes of administration (Figures N1 and N2). The administration of dibromoacetic acid in an aqueous solution averted any dissolution phase, which is the rate-limiting step for solid dosage formulations such as dosed feed, and thereby precluded the presence of a lag time in the plasma concentration time profile. A one-compartment model with no lag phase and first-order absorption and elimination provided the best fit to the plasma concentration versus time profiles. The absorption rate constant and absorption half-life values observed with gavage administration very closely resembled the elimination rate constant and elimination half-life values observed with intravenous administration. In addition, the elimination rate constant and elimination half-life values observed with gavage administration were 4- to 5-fold greater than those associated with intravenous administration, confirming flip-flop kinetics. Flip-flop kinetics are commonly observed with test articles that undergo very fast elimination and indicate that the toxicokinetic parameters determined for the absorption phases are actually estimates of the elimination phase and vice versa.

Based on the flip-flop model findings for rats, the absorption rate constant values ranged from 0.87 to 0.62 $hours^{-1}$ for males and 0.80 to 0.71 $hours^{-1}$ for females. Corresponding absorption half-life values for all dose groups with both sexes ranged from 0.8 to 1.2 hours (Table N1). Elimination rate constants ranged from 4.1 to 6.2 $hours^{-1}$ for males and 10.0 to 7.0 $hours^{-1}$ for females. Corresponding elimination half-lives were similar across both sexes and all dose groups and ranged from 0.1 to 0.2 hours. Bioavailability, from comparison of the AUCs for intravenous and gavage administration, ranged from approximately 43% to 61% for males and 64% to 91% for females.

Very similar observations to those in rats were made with the mouse plasma concentration versus time profiles. Absorption rate constants for male mice ranged from 1.9 to 0.40 $hours^{-1}$ and ranged from 2.1 to 0.35 $hours^{-1}$ in females based on the flip-flop model. Corresponding absorption half-life values ranged from 0.4 to 1.8 hours for males and 0.3 to 2.0 hours for females and increased with increasing dose (Table N2). Elimination rate constants ranged from 4.9 to 11.0 $hours^{-1}$ for males (not consistent with dose) and were 8.6 to 17.1 $hours^{-1}$ in females.

Across both sexes and all dose groups, the elimination half-lives ranged from 0.04 to 0.12 hours. Bioavailability in mice was approximately 11% to 44% and increased with dose.

In the current toxicokinetic studies in rats and mice, volume of distribution, clearance, and $AUC_{infinity}$ values as typically calculated were invalid because these parameters are a function of the elimination phase, which is not the terminal linear phase in these studies. These values, therefore, are not reported for these studies. AUC values not affected by the extrapolation of the terminal linear phase increased with dose in both sexes of both species.

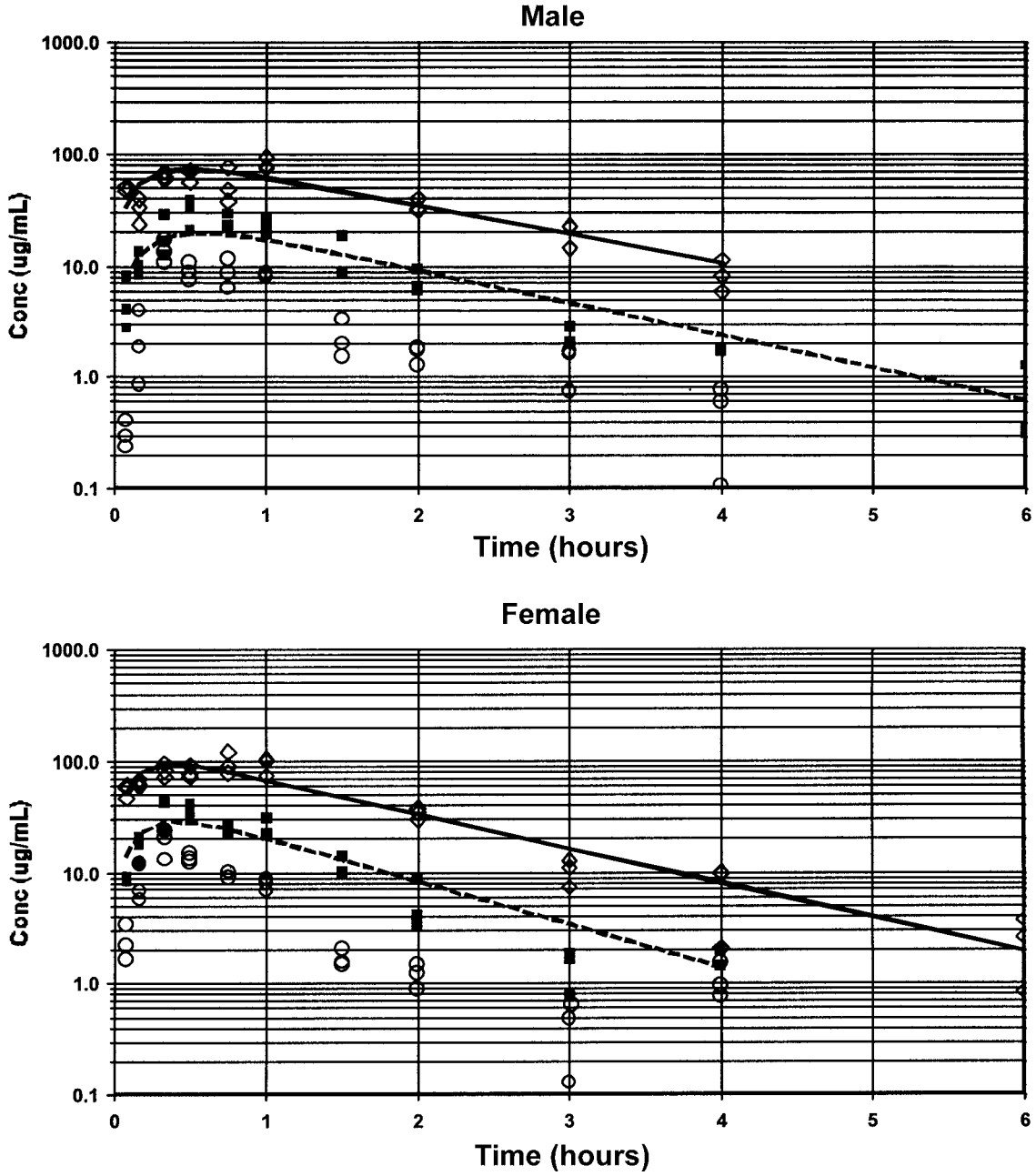

FIGURE N1
Plasma Concentrations of Dibromoacetic Acid in Male and Female F344/N Rats After a Single Gavage Dose of 25, 50, or 125 mg/kg Dibromoacetic Acid
Lines represent the best-fit curves (WinNONLIN®) plotted through the observed data points; data points represent plasma samples from individual rats.
(Observed data: ○ – 25 mg/kg; ■ – 50 mg/kg; ◇ – 125 mg/kg)

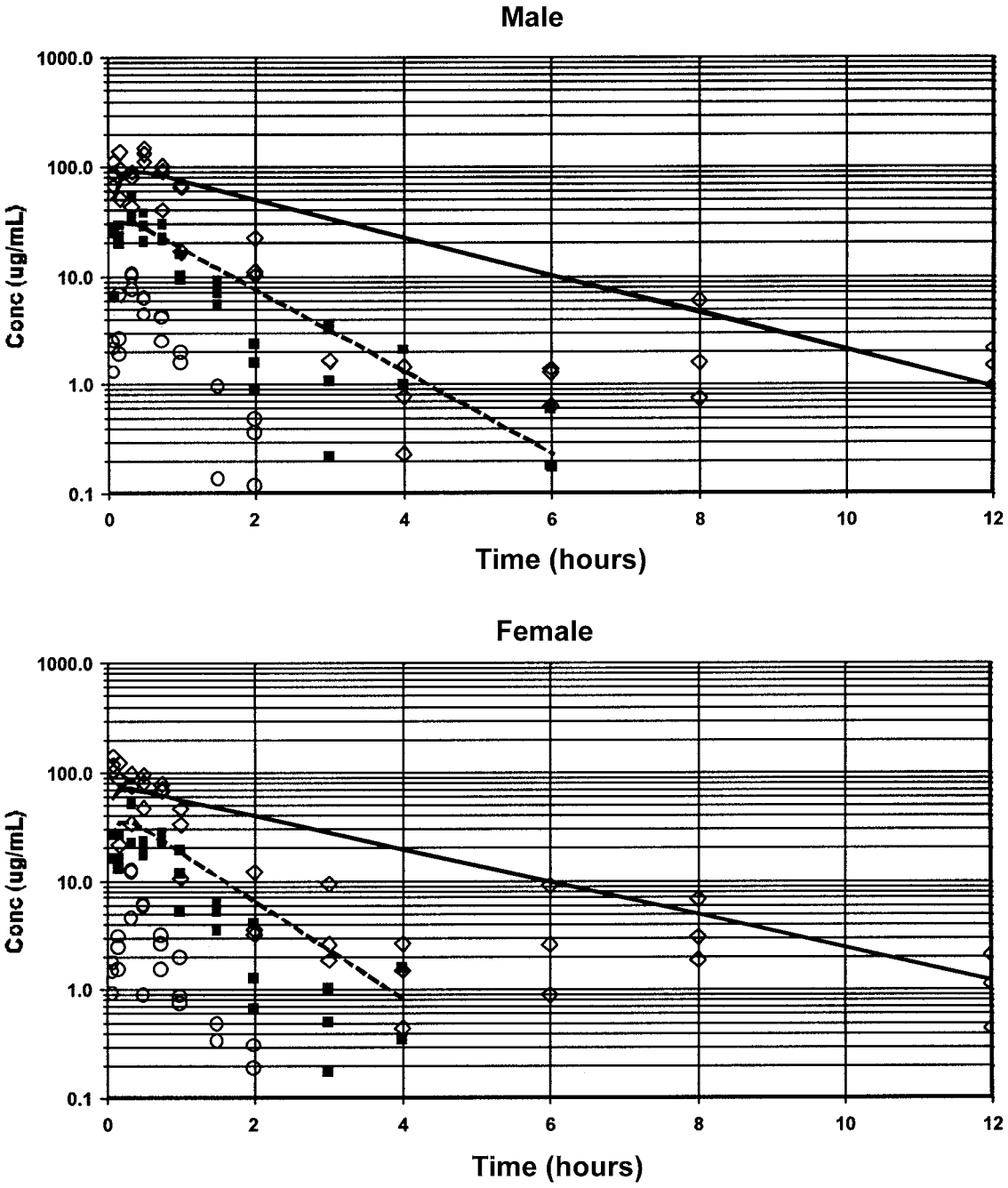

FIGURE N2
Plasma Concentrations of Dibromoacetic Acid in Male and Female B6C3F$_1$ Mice After a Single Gavage Dose of 70, 175, or 350 mg/kg Dibromoacetic Acid
Lines represent the best-fit curves (WinNONLIN®) plotted through the observed data points; data points represent plasma samples from individual mice.
(Observed data: ○ – 70 mg/kg; ■ – 175 mg/kg; ◇ – 350 mg/kg)

TABLE N1
Toxicokinetic Parameter Estimates for the Elimination of Dibromoacetic Acid from the Plasma of F344/N Rats After a Single Gavage Dose of Dibromoacetic Acid[a]

Parameter	25 mg/kg	50 mg/kg	125 mg/kg
Male			
C_{max} (µg/mL)	10.5 ± 1.3	24.2 ± 2.4	77.5 ± 5.9
C_{max}/dose	0.42 ± 0.052	0.48 ± 0.048	0.62 ± 0.00
$AUC_{0\text{-}1\ hour}$ [(µg • hours)/mL]	7.77	20.6	54.7
$AUC_{0\text{-}1\ hour}$/dose	0.31	0.41	0.44
Absorption half-life (hours)[b]	0.168 ± 0.064	0.156 ± 0.046	0.112 ± 0.028
Elimination half-life (hours)[b]	0.798 ± 0.117	0.945 ± 0.079	1.19 ± 1.09
Female			
C_{max} (µg/mL)	14.9 ± 2.0	29.2 ± 2.7	94.9 ± 7.7
C_{max}/dose	0.59 ± 0.080	0.58 ± 0.054	0.76 ± 0.062
$AUC_{0\text{-}1\ hour}$ [(µg • hours)/mL]	10.8	26.3	76.8
$AUC_{0\text{-}1\ hour}$/dose	0.43	0.53	0.61
Absorption half-life (hours)[b]	0.069 ± 0.036	0.130 ± 0.037	0.098 ± 0.027
Elimination half-life (hours)[b]	0.869 ± 0.11	0.771 ± 0.071	0.982 ± 0.059

[a] Data are presented as mean (AUCs) or mean ± standard error. C_{max} = maximum plasma concentration; $AUC_{0\text{-}1\ hour}$ = area under the plasma concentration versus time curve from time 0 to 1 hour.
[b] Due to flip-flop kinetics, absorption half-life estimates are actually elimination half-life estimates and vice versa.

TABLE N2
Toxicokinetic Parameter Estimates for the Elimination of Dibromoacetic Acid from the Plasma of $B6C3F_1$ Mice After a Single Gavage Dose of Dibromoacetic Acid[a]

Parameter	70 mg/kg	175 mg/kg	350 mg/kg
Male			
C_{max} (µg/mL)	6.04 ± 0.75	32.2 ± 4.1	91.1 ± 13.9
C_{max}/dose	0.086 ± 0.011	0.184 ± 0.023	0.26 ± 0.040
$AUC_{0\text{-}20\ minutes}$ [(µg • hours)/mL]	1.42	8.03	24.3
$AUC_{0\text{-}20\ minutes}$/dose	0.020	0.046	0.069
Absorption half-life (hours)[b]	0.118 ± 0.046	0.063 ± 0.031	0.087 ± 0.048
Elimination half-life (hours)[b]	0.359 ± 0.058	0.798 ± 0.056	1.75 ± 0.16
Female			
C_{max} (µg/mL)	6.75 ± 1.21	36.4 ± 5.12	72.2 ± 10.7
C_{max}/dose	0.373 ± 0.017	0.208 ± 0.029	0.206 ± 0.031
$AUC_{0\text{-}20\ minutes}$ [(µg • hours)/mL]	1.22	7.43	24.7
$AUC_{0\text{-}20\ minutes}$/dose	0.017	0.042	0.070
Absorption half-life (hours)[b]	0.081 ± 0.041	0.065 ± 0.035	0.040 ± 0.037
Elimination half-life (hours)[b]	0.330 ± 0.051	0.671 ± 0.066	1.99 ± 0.20

[a] Data are presented as mean (AUCs) or mean ± standard error. C_{max} = maximum plasma concentration; $AUC_{0\text{-}20\ minutes}$ = area under the plasma concentration versus time curve from time 0 to 20 minutes.
[b] Due to flip-flop kinetics, absorption half-life estimates are actually elimination half-life estimates and vice versa.