NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 396

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MONOCHLOROACETIC ACID

(CAS NO. 79-11-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF MONOCHLOROACETIC ACID

(CAS NO. 79-11-8)

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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CONTRIBUTORS

National Toxicology Program

K.M. Abdo, Ph.D.
C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.W. Bristol, Ph.D.
S.L. Eustis, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
R.A. Griesemer, D.V.M., Ph.D.
J.K. Haseman, Ph.D.
M.P. Jokinen, D.V.M.
M.M. McDonald, D.V.M., Ph.D.
R.L. Melnick, Ph.D.
G.N. Rao, D.V.M., Ph.D.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

International Research and Development

Conducted studies and evaluated tissues

B.M. Phillips, Ph.D., Principal Investigator
M. Blair, Ph.D.
A.D. Boothe, D.V.M., Ph.D.
J. Laveglia, Ph.D.
K.P.C. Nair, B.V.Sc., M.S.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assessment

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

Biotechnical Services, Inc.

Prepared Technical Report

L.G. Cockerham, Ph.D., Principal Investigator
J.L. Elledge, B.A.
K.D. Mencer, B.A.

NTP Pathology Working Group

Evaluated slides and prepared pathology reports on rats
27 September 1988

S. Grumbein, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
R. Cattley, V.M.D., M.S.
North Carolina State University
M.R. Elwell, D.V.M., Ph.D.
National Toxicology Program
K. Heider, D.V.M.
CIBA-Geigy, Switzerland
P.K. Hildebrandt, D.V.M., Study Pathologist
PATHCO
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
J. Peckham, D.V.M.
Experimental Pathology Laboratories, Inc.
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

NTP Pathology Working Group

Evaluated slides and prepared pathology reports on mice
18 July 1989

M.A. Stedham, D.V.M., M.S., Chair
Pathology Associates, Inc.
R. Cattley, V.M.D., M.S.
North Carolina State University
M.R. Elwell, D.V.M., Ph.D.
National Toxicology Program
D. Goodman, V.M.D., Study Pathologist
PATHCO
M.P. Jokinen, D.V.M.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.,
Pathology Associates, Inc.

Integrated Laboratory Systems

Performed quality assurance audits

J.C. Bhandari, D.V.M., Ph.D., Principal Investigator

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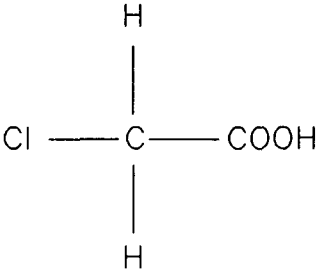
ABSTRACT



MONOCHLOROACETIC ACID

CAS No. 79-11-8

Chemical Formula: $C_2H_3ClO_2$ Molecular Weight: 94.5

Synonyms: Chloroacetic acid, α-chloroacetic acid, chloroethanoic acid

Monochloroacetic acid, a colorless crystalline material, is used as a postemergence contact herbicide and as an intermediate in the synthesis of other organic compounds. Toxicology and carcinogenicity studies were conducted by administering monochloroacetic acid (99% pure) in deionized water by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex once daily, 5 days per week for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma L5178Y cells, Chinese hamster ovary cells, and *Drosophila melanogaster*.

16-Day Studies
Groups of five rats of each sex received 0, 7.5, 15, 30, 60, or 120 mg monochloroacetic acid/kg body weight. Doses administered to mice were 0, 15, 30, 60, 120, or 240 mg/kg to groups of five males and 0, 30, 60, 120, 240, or 480 mg/kg to groups of five females. One of five male rats given 120 mg/kg died during the studies. Clear nasal discharge, lacrimation, or both, were observed in all groups of male and female rats receiving monochloroacetic acid. No compound-related gross lesions were observed in rats. All male mice given 240 mg/kg and all females given 240 or 480 mg/kg died during the studies. Hypoactivity, piloerection, ataxia, and lacrimation were observed in mice given 240 or 480 mg/kg. No compound-related gross lesions were observed in mice at necropsy.

13-Week Studies
Groups of 20 rats of each sex received 0, 30, 60, 90, 120, or 150 mg/kg monochloroacetic acid, and groups of 20 mice of each sex received doses of 0, 25, 50, 100, 150, or 200 mg/kg. Three to five animals in each dose group were killed at weeks 4 and 8 for the evaluation of hematology parameters. Compound-related deaths occurred in rats in the three highest dose groups (all males given 120 or 150 mg/kg, 9/10 males given 90 mg/kg, and all females given 90 to 150 mg/kg) and in mice given 200 mg/kg (all males and 2/10 females). Final mean body weights of surviving rats and mice receiving monochloroacetic acid were similar to those of controls. In rats, dose-related increases in blood urea nitrogen, alanine aminotransferase, and aspartate aminotransferase levels were observed, and relative liver and kidney weights were elevated. There were no compound-related changes in the various hematologic or clinical pathology parameters in mice. A dose-related increase in the incidence and severity of cardiomyopathy was observed in male and female rats receiving monochloroacetic acid, and hepatocellular cytoplasmic vacuolization was observed in the high-dose mice that died during the studies.

2-Year Studies
Based on the mortality and compound-related histopathologic lesions observed in the 13-week studies, doses selected for the 2-year studies of monochloroacetic acid were 0, 15, or 30 mg/kg, administered to groups of 70 rats of each sex, and 0, 50, or 100 mg/kg, administered to groups of 60 mice of each sex. Interim evaluations were conducted on 10 rats per dose group after 6 months of treatment with monochloroacetic acid and on seven rats per dose group after 15 months of treatment.

Body Weight and Survival in the 2-Year Studies
Mean body weights of low- and high-dose female and low-dose male rats receiving monochloroacetic acid were within 10% of those of controls throughout the studies; however, after week 30, the mean body weights of high-dose male rats were 4% to 8% less than those of controls. In mice, the mean body weights of dosed males were similar to controls, but those of low- and high-dose females were 6% to 10% less than control values after week 52. Survival of high-dose male and dosed female rats and high-dose male mice was significantly lower than that of controls (male rats: control, 27/53; low-dose, 21/53; high-dose, 16/53; female rats: 37/53; 19/53; 26/53; male mice: 46/60; 39/60; 21/60; female mice: 42/60; 40/60; 44/60).

Neoplasms and Nonneoplastic Lesions in the 2-Year Studies
There was no compound-related increase in the incidence of neoplasms or nonneoplastic lesions in rats given monochloroacetic acid for 2 years. The incidence of uterine stromal polyps in low- and high-dose female rats was slightly higher than that in controls (2/60; 7/57; 10/60). However, the incidence in the controls was unusually low, and those in the dosed groups were well within the range for NTP historical controls (mean: 21%, range: 10%-38%). Further, because the only malignant stromal neoplasm occurred in a control animal, the polyps were not considered to be related to the administration of monochloroacetic acid. Similarly, there was no monochloroacetic acid-related increase in the incidence of neoplasms in male or female mice, and malignant lymphoma occurred with a significant negative trend in dosed female mice. Increases in the incidence of inflammation of the mucosa of the nasal passages, respiratory epithelial metaplasia of the olfactory epithelium of the nose, and focal squamous cell hyperplasia of the forestomach occurred in dosed male and female mice.

Genetic Toxicology
Monochloroacetic acid was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98, with or without exogenous metabolic activation (S9). It induced trifluorothymidine resistance in L5178Y cells in the absence of S9 and induced sister chromatid exchanges without S9 in Chinese hamster ovary cells. Monochloroacetic acid did not induce a significant increase in chromosomal aberrations in Chinese hamster ovary cells, with or without S9. Monochloroacetic acid administered in feed was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster;* however, when it was administered by injection, the results were equivocal.

Conclusions
Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** for monochloroacetic acid in male or female F344/N rats given 15 or 30 mg/kg. There was *no evidence of carcinogenic activity* for monochloroacetic acid in male or female $B6C3F_1$ mice given 50 or 100 mg/kg.

Monochloroacetic acid administration was associated with inflammatory lesions of the nasal mucosa, metaplasia of the olfactory epithelium, and squamous cell hyperplasia of the forestomach in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

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

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 15, or 30 mg/kg in deionized water by gavage 5 days per week	0, 15, or 30 mg/kg in deionized water by gavage 5 days per week	0, 50, or 100 mg/kg in deionized water by gavage 5 days per week	0, 50, or 100 mg/kg in deionized water by gavage 5 days per week
Body weights	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups lower than controls
2-Year survival rates	27/53, 21/53, 16/53	37/53, 19/53, 26/53	46/60, 39/60, 21/60	42/60, 40/60, 44/60
Nonneoplastic effects	None	None	Inflammation of nasal mucosa (3/60, 7/59, 24/60); Metaplasia of olfactory epithelium (0/60, 3/59, 2/60) Squamous hyperplasia of the forestomach (5/60, 2/60, 13/60)	Inflammation of nasal mucosa (5/60, 15/60, 31/60; Metaplasia of olfactory epithelium (2/60, 5/60, 17/60); Squamous hyperplasia of the forestomach (5/60, 8/59, 15/60)
Neoplastic effects	None	None	None	None
Uncertain findings	None	None	None	Malignant lymphoma (29/60, 18/60, 13/60)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative with or without S9 in strains TA100, TA1535, TA1537, or TA98			
L5178Y mouse lymphoma gene mutation:	Positive without S9			
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with S9			
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:	Negative with or without S9			
Sex-linked recessive lethal mutations *Drosophila melanogaster* male germ cells:	Negative when administered in feed Equivocal when administered by injection			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on monochloroacetic acid on November 20, 1990 are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

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

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D., Chair
Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corp.
East Millstone, NJ

Jay I. Goodman, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

Daniel S. Longnecker, M.D., Principal Reviewer
Department of Pathology
Dartmouth Medical School, Hanover, NH

Ellen K. Silbergeld, Ph.D.*
University of Maryland Medical School
Baltimore, MD

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D., Principal Reviewer
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderly Park, England

Gary P. Carlson, Ph.D.
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, D.V.M., Ph.D., Principal Reviewer
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, D.V.M.
Consultants in Veterinary Pathology
Murrysville, PA

Lois Swirsky Gold, Ph.D.
Lawrence Berkeley Laboratory
University of California
Berkeley, CA

David W. Hayden, D.V.M., Ph.D.
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

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

Barbara McKnight, Ph.D.
Department of Biostatistics
University of Washington
Seattle, WA

Lauren Zeise, Ph.D.
California Department of Health Services/RCHAS
Berkeley, CA

*Did not attend

SUMMARY OF PEER REVIEW COMMENTS

On November 20, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of monochloroacetic acid received public review by the National Toxicology Program (NTP) Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of monochloroacetic acid by discussing the uses of this compound and the rationale for its study, describing the experimental design, reporting on survival and body weight effects, and commenting on nonneoplastic lesions that were observed. The conclusions were *no evidence of carcinogenic activity* of monochloroacetic acid for male or female F344/N rats or B6C3F$_1$ mice.

Dr. Davis, the first principal reviewer, agreed with the conclusions. He commented that a maximum tolerated dose may not have been reached for female mice because the difference between control and high-dose group final mean body weights was only 6%. He further noted that from week 53 to week 103 the difference in mean body weights between the two groups was only 9%. Dr. S.L. Eustis, NIEHS, explained that a consistent decrement in body weight over a long period of time usually represents a toxic effect, even if the decrement is less than 10%, as in these studies. Dr. J.K. Haseman, NIEHS, added that the nonneoplastic lesions of the nasal cavity and forestomach observed in this study suggested that a maximum tolerated dose had been achieved.

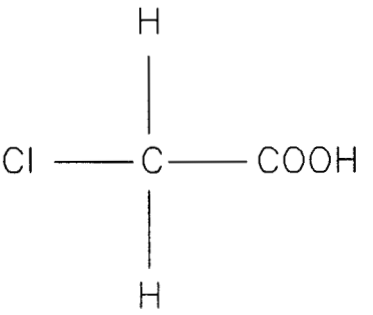
Dr. Longnecker, the second principal reviewer, agreed with the conclusions.

Dr. Ashby, the third principal reviewer, agreed with the conclusions. He noted that the genetic toxicity profile continued a trend established in earlier studies, namely, no structural alert, no mutagenicity in *Salmonella*, and no clastogenicity in Chinese hamster ovary cells, but induction of mutations in L5178Y cells and of sister chromatid exchanges in Chinese hamster ovary cells. He added that this pattern confirmed that the latter two protocols were not correlated with *in vivo* carcinogenicity.

There was some discussion about the forestomach lesions in mice and, in particular, about the increased incidence of squamous cell papillomas in females. The discussion of the papillomas centered on whether the significant increase in incidence of hyperplasia in the high-dose group reflected a preneoplastic effect or focal irritation due to gavage with an irritating substance. The NTP staff supported the latter position.

Dr. Davis moved that the Technical Report on monochloroacetic acid be accepted with the revisions discussed and the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Longnecker seconded the motion, which was accepted unanimously with 11 votes.

INTRODUCTION



MONOCHLOROACETIC ACID

CAS No. 79-11-8

Chemical Formula: $C_2H_3ClO_2$ Molecular Weight: 94.5

Synonyms: Chloroacetic acid, α-chloroacetic acid, chloroethanoic acid

PHYSICAL AND CHEMICAL PROPERTIES, USE, AND EXPOSURE

Monochloroacetic acid, a colorless crystalline material, is used as a postemergence contact herbicide and as an intermediate in the synthesis of other organic compounds (Sax, 1981; *Merck Index*, 1983). Monochloroacetic acid exists in three polymorphic forms, which have melting points of 50°, 56°, and 63° C. The commercial compound melts at 61° to 63° C and boils at 189° C (*Merck Index*, 1983). Monochloroacetic acid is highly soluble in water and is soluble in organic solvents; its vapor pressure is 1 mm Hg at 43° C. With a pK_a of 2.86 (Fassett, 1967), monochloroacetic acid is a weak acid, with an acidity greater than that of acetic acid, but less than that of di- or trichloroacetic acid. Monochloroacetic acid is usually synthesized by chlorination of acetic acid. In addition, haloacetic acids, including monochloroacetic acid, are byproducts of water chlorination (Krasner *et al.*, 1989).

Potentially 11,500 workers in the United States are exposed to monochloroacetic acid (NIOSH, 1990). Next to the trihalomethanes, the haloacetic acids are the most commonly detected disinfection byproducts in drinking water supplies in the United States (Krasner *et al.*, 1989). The median concentration of haloacetic acids in 35 water utilities was 19 μg/L (19 ppb); the median concentration of monochloroacetic acid was about 1 μg/L.

METABOLISM AND DISPOSITION

In Sprague-Dawley rats administered an oral dose of 53 or 162 mg/kg ^{14}C-monochloroacetate, concentrations of ^{14}C were greater in the liver and kidney than in the plasma (Hayes *et al.*, 1973). Levels of radioactivity in the heart and brain were similar to that in the plasma. Peak plasma levels of radioactivity were reached approximately 30 minutes after administration of the compound. At 17 hours, approximately 50% of the administered radioactive dose had been recovered in the urine.

Yllner (1971a) reported that 3 days following intraperitoneal injection of 2 mg monochloroacetic-1-^{14}C acid in mice, 82% to 88% of the

administered dose was eliminated in the urine, 8% was eliminated in the expired air as CO_2, and less than 3% was eliminated in the feces; 2% to 3% of the administered dose remained in the animal. Of the radiolabel recovered in the urine, 6% to 22% was present as the parent compound. Metabolites of monochloroacetic acid identified in the urine included S-carboxymethylcysteine (33%-43% free and 1%-6% conjugated), thiodiacetic acid (thiodiglycolic acid) (33%-42%), glycolic acid (3%-5%), and oxalic acid (0.1%-0.2%). In separate experiments in mice, thiodiglycolic acid was found to be the major urinary metabolite of S-carboxymethylcysteine, and most of the glycolate was oxidized to carbon dioxide.

In Wistar rats given 50 mg/kg monochloroacetic acid by gavage, thiodiglycolic acid was identified as the major urinary metabolite, accounting for 60% of the administered dose (Green and Hathway, 1975). A greater percentage of administered monochloroacetic acid was excreted as thiodiglycolic acid in rats than in mice; in both species most of the remainder of the dose was excreted as S-carboxymethylcysteine (Jones and Hathway, 1978).

Monochloroacetic acid has been identified as a urinary metabolite of vinyl chloride (chloroethylene) (Bartsch and Montesano, 1975; Bartsch *et al.*, 1976), vinylidene chloride (1,1-dichloroethylene) (Hathway, 1977; Jones and Hathway, 1978), 1,2-dichloroethane (Yllner, 1971b), and 1,1,2-trichloroethane (Yllner, 1971c). Because the profile of urinary metabolites for mice exposed to 1,2-dichloroethane and 1,1,2-trichloroethane was qualitatively and quantitatively similar to that for mice exposed to monochloroacetic acid, Yllner (1971a,b) suggested that the metabolism of 1,2-dichloroethane and of 1,1,2-trichloroethane occurs mainly via the formation of monochloroacetic acid.

TOXICITY

Effects in Humans

Monochloroacetic acid is a strong irritant to the skin, eyes, and mucous membranes (Morrison and Leake, 1941; Sax, 1984). Aqueous solutions of monochloroacetic acid at concentrations up to 1% produced no observable effect on human skin (Morrison and Leake, 1941). No adverse effects were detected in three human volunteers who drank 300 mL of a 0.05% water solution of monochloroacetic acid for 60 days (Morrison and Leake, 1941).

Animal Toxicity

Monochloroacetic acid is more acutely toxic to rats and mice than is acetic acid, dichloroacetic acid, or trichloroacetic acid. Oral LD_{50} values for aqueous solutions of monochloroacetic acid adjusted to pH 6 to 7 were 76 mg/kg in rats, 255 mg/kg in mice, and 80 mg/kg in guinea pigs (Woodward *et al.*, 1941). Morrison and Leake (1941) reported that the oral LD_{50} of monochloroacetic acid was 165 mg/kg in mice; death in this study was due to respiratory paralysis. In male Sprague-Dawley rats, the acute oral toxicities (LD_{50}) of aqueous solutions of monohaloacetates were ranked as: monofluoroacetate (5 mg/kg) > monoiodoacetate (60 mg/kg) > monochloroacetate (108 mg/kg) (Hayes *et al.*, 1973). Signs of chloroacetate toxicity in rats included dipsesis, clonic and tonic convulsions, and respiratory depression. In mice, the acute oral toxicities (LD_{50}) of aqueous solutions of monohaloacetates were ranked as: monoiodoacetate (63 mg/kg) > monobromoacetate (100 mg/kg) > monochloroacetate (165 mg/kg) (Fuhrman *et al.*, 1955).

In a study by Davis and Berndt (1987), oral administration of neutralized aqueous solutions of monochloroacetate to male or female Sprague-Dawley rats at a single dose of 94 mg/kg had no effect on body weight, urine volume, or urine composition (osmolality, sodium, potassium, glucose, and protein). Doses of 282 mg/kg or higher were lethal.

Fuhrman *et al.* (1955) did not observe exposure-related gross or microscopic lesions in male Slonaker-Wistar rats fed diets containing 0.005% to 0.1% monochloroacetic acid for 30 weeks (tissues examined included heart, liver, spleen, adrenal gland, kidney, lung, stomach, intestine, pancreas, thyroid gland, bladder, and testis). No exposure-related gross or microscopic lesions were observed in mice given drinking water containing 0.05% or 0.5% monochloroacetic acid for 44 weeks (Morrison and Leake, 1941); growth retardation observed in the mice receiving 0.5% monochloroacetic acid was attributed to the reduced palatability of the acidic solution.

In studies of the acute toxicity of water pollutants to *Daphnia magna*, exposure to approximately 100 mg/L (100 ppm) of monochloroacetic acid for 24 hours reduced by 50% the number of animals that could still swim (Kuhn *et al.*, 1989a). In a 21-day *Daphnia* reproduction test, the concentration of monochloroacetic acid at which there was

no observed effect was found to be 32 mg/L (Kuhn *et al.*, 1989b).

Quick *et al.* (1983) reported that in two separate incidents cattle or sheep were poisoned after exposure to sodium monochloroacetate. The estimated fatal dose of this herbicide was in the range of 17 to 68 mg/kg. Extensor paralysis of the limbs, tremors, and convulsions were observed in three animals prior to death. The neurotoxic potential of monochloroacetic acid was also demonstrated in Swiss-Webster mice when front paw rigidity was observed in animals that survived an oral LD_{80} dose of 380 mg/kg (Berardi *et al.*, 1987). Furthermore, because concentrations of intravenously administered ^{14}C-inulin or ^{3}H-dopamine were greater in brains of dosed animals than in controls, it was suggested that monochloroacetic acid impairs the functional integrity of the brain microvasculature.

Carcinogenicity

Monochloroacetic acid was not carcinogenic to $B6C3F_1$ mice or $B6AKF_1$ mice when applied subcutaneously at a dose of 100 mg/kg per day or given by gavage (46.4 mg/kg per day) for 3 weeks and in the feed at a higher concentration (149 mg/kg per day) for an additional 78 weeks (Innes and Ulland, 1968). Because a small number of animals was used (18 animals/sex per strain) and because the study duration was short (82 weeks), this study would be considered inadequate by current standards. In 61-week drinking water studies, dichloroacetic acid and trichloroacetic acid were carcinogenic in male $B6C3F_1$ mice (Herren-Freund *et al.*, 1987). Treatment with these compounds was associated with an increased incidence of neoplasms of the liver and caused significant increases in liver weight. Long-term studies have not been reported for dichloroacetic acid or trichloroacetic acid in other species. DeAngelo *et al.* (1989) suggested that the induction of liver tumors in mice by dichloroacetic acid or trichloroacetic acid might be related to the induction of peroxisome proliferation in this species. These compounds caused much greater increases in liver weight and hepatic peroxisome proliferation in mouse strains ($B6C3F_1$, Swiss-Webster, C3H, and C57BL/6) than in rat strains (Sprague-Dawley, F344/N, and Osborne-Mendel). Exposure of $B6C3F_1$ mice or Sprague-Dawley rats for 14 days to drinking water containing 0.1% to 0.3% monochloroacetic acid (average daily intake of monochloroacetic acid was approximately 500 mg/kg per day) did not result in increases in liver weight or induction of peroxisome proliferation (DeAngelo *et al.*, 1989). Nelson *et al.* (1989) reported that a single oral dose (500 mg/kg) of dichloroacetic acid or trichloroacetic acid in $B6C3F_1$ mice induced hepatic DNA single strand breaks that were independent of peroxisome proliferation; single strand breaks were increased between 1 and 4 hours after dosing, prior to evidence of peroxisome induction. Thus, the critical early events in the induction of liver tumors by these compounds have not been resolved.

A number of chlorinated hydrocarbons that are metabolized to monochloroacetic acid have been found to be carcinogenic in laboratory animals. These include vinyl chloride (IARC, 1987), 1,2-dichloroethane (NCI, 1978a), and 1,1,2-trichloroethane (NCI, 1978b). Vinyl chloride induced tumors of the mammary gland, lung, Zymbal's gland, skin, and liver (hemangiosarcomas); 1,2-dichloroethane induced tumors of the forestomach, skin, circulatory system (hemangiosarcomas), mammary gland, liver, lung, and uterus; and 1,1,2-trichloroethane induced tumors of the liver and adrenal gland.

Genetic Toxicity

The genotoxicity test data for monochloroacetic acid are limited, but indicate that the potential for DNA damage and mutagenicity is probably low. Monochloroacetic acid did not cause preferential killing of a DNA repair-deficient strain of *Escherichia coli* (WP100) over the wild-type strain (WP2) (Mamber *et al.*, 1983) and it was inactive when tested for prophage induction in a lysogenic strain of *E. coli* K12 (Mamber *et al.*, 1984). These findings indicated that exposure to monochloroacetic acid did not induce DNA damage in these test systems. In addition, monochloroacetic acid did not induce *umu* gene expression in *Salmonella typhimurium* strain TA1535/pSK1002, a strain containing a fused *umuC-lacZ* gene. The genetic configuration of this strain allows indirect measurement of *umuC* gene activity through the monitoring of the production of β-galactosidase, encoded by the *lacZ* gene (Nakamura *et al.*, 1987). The *umu* gene is activated in response to DNA damage, and because exposure to monochloroacetic acid did not result in an increase in β-galactosidase, it was inferred that a DNA repair response was not induced. Monochloroacetic acid was not mutagenic in any of several strains of *S. typhimurium* (base-pair substitution and frameshift mutants), with or without

exogenous metabolic activation (Bartsch and Montesano, 1975; McCann *et al.*, 1975a,b; Bartsch *et al.*, 1976; Rannug *et al.*, 1976; Mortelmans *et al.*, 1986), or in Chinese hamster V79-4 cells (Bartsch and Montesano, 1975). However, a positive response was obtained in the mouse lymphoma L5178Y cell assay for the induction of trifluorothymidine resistance, with or without S9 activation (Amacher and Turner, 1982; McGregor *et al.*, 1987).

Monochloroacetic acid did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster lung fibroblast cells in the presence or in the absence of S9 activation (Sawada *et al.*, 1987). In Chinese hamster ovary cells, no induction of aberrations was observed after treatment with monochloroacetic acid in the presence or in the absence of S9, but a dose-related increase in sister chromatid exchanges was observed without S9 (Galloway *et al.*, 1987). There is one unconfirmed report of induced meiotic abnormalities in pollen mother cells of *Vicia faba* plants sprayed with an aqueous solution of monochloroacetic acid (0.05%); Amer and Ali (1980) described increases in lagging chromosomes, chromosome stickiness, and chromosome fragmentation when treatment occurred at the seedling or the flowering stages of development.

The only mutagenicity information available on metabolites of monochloroacetic acid consists of one report of a positive response in the *Salmonella* assay (TA100) with glycolic acid, a minor metabolite (Yamaguchi and Nakagawa, 1983).

Mutagenicity data from the testing of structural analogues, the di- and trichloroacetic acids, agree with the negative results obtained with monochloroacetic acid in the *Salmonella* gene mutation test (Bignami *et al.*, 1977; Sato *et al.*, 1985). There is one report of the induction of cytogenetic abnormalities in bone marrow and sperm cells of Swiss mice exposed by intraperitoneal injection to doses of 125, 250, or 500 mg/kg trichloroacetic acid (Bhunya and Behera, 1987); these data are difficult to interpret, however, due to the description of the experimental methods used in the study and the classification of the abnormalities scored.

STUDY RATIONALE

Monochloroacetic acid was nominated by the United States Environmental Protection Agency for toxicology and carcinogenesis studies because of its large production volume, its presence in drinking water supplies, and the lack of previous studies to determine its carcinogenic potential. Furthermore, monochloroacetic acid is a metabolite of a number of known carcinogens including vinyl chloride, 1,2-dichloroethane, and 1,1,2-trichloroethane. The oral route of administration was selected because that is the most common route of human exposure to this chemical. Gavage administration was chosen to maximize the dose given.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MONOCHLOROACETIC ACID

Monochloroacetic acid was obtained from American Hoechst (Somerville, NJ) in one lot (lot no. C035826). Purity, identity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) and confirmed by the study laboratory (Appendix H). The study chemical, a white solid, was identified as monochloroacetic acid by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Its purity was determined to be approximately 99% by Karl Fischer water analysis, elemental analysis, thin layer chromatography, gas chromatography, and potentiometric titration. Stability studies using gas chromotography showed that the bulk chemical was stable for at least 2 weeks at temperatures up to 60° C. The bulk chemical was stored at room temperature at the study laboratory throughout the study period. The stability of the bulk chemical was monitored by potentiometric titration and by flame-ionization gas chromatography periodically at the study laboratory during all phases of the studies. No change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The gavage route of administration was chosen for these studies because monochloroacetic acid was unstable in feed formulations, as determined by gas chromatographic analysis. Throughout the studies, the dose formulations were prepared by mixing appropriate amounts of monochloroacetic acid and deionized water (Appendix H, Table H1). Stability studies conducted by the analytical chemistry laboratory and by the study laboratory confirmed the stability of monochloroacetic acid solutions for at least 3 weeks. During the studies, the dose formulations were stored at room temperature for no longer than 3 weeks.

The study laboratory conducted periodic analyses of the monochloroacetic acid dose formulations using gas chromatographic procedures as described in Appendix H. During the 2-year studies, the dose formulations were within 10% of the target concentrations 93% (28/30) of the time for rats and 100% (28/28) of the time for mice (Tables H3a and H3b). Results of periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Tables H4a and H4b).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI). Before the studies began, mice were quarantined for 13 days, and rats were quarantined for 15 days. The rats were 5 to 6 weeks old when placed on study and the mice were 7 to 8 weeks old.

Groups of five rats of each sex were administered 0, 7.5, 15, 30, 60, or 120 mg/kg monochloroacetic acid in deionized water by gavage once daily for a total of 12 dose days over a 16-day period. Groups of five mice of each sex received monochloroacetic acid in deionized water on the same schedule, but at doses of 0, 15, 30, 60, 120, or 240 mg/kg for males and 0, 30, 60, 120, 240, or 480 mg/kg for females. Animals were housed five per cage. Water and feed were available *ad libitum*.

Animals were weighed prior to initiation of chemical administration, on days 7 and 14 during treatment, and at study termination. Animals were observed twice daily for morbidity and mortality. Observations for signs of toxicity were made 0.5, 1, 2, 3, and 4 hours after dosing on the first two dose days and once daily, except on weekends, for the remainder of the studies. All animals were necropsied, including those dying before the end of the studies. Organ weights were obtained for brain, heart, kidney, liver, lungs, and thymus for all animals surviving to study termination. Histopathology was performed on selected animals and tissues. Further experimental details are presented in Table 1.

13-WEEK STUDIES

Thirteen-week studies were designed to evaluate the cumulative toxic effects of repeated exposure to

monochloroacetic acid and to determine the doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 13 days, distributed to weight classes, and assigned to groups according to tables of random numbers. The rats were 6 to 7 weeks old and the mice were 7 to 8 weeks old when placed on study. Further experimental details are provided in Table 1.

Groups of 20 rats of each sex were administered 0, 30, 60, 90, 120, or 150 mg/kg monochloroacetic acid in deionized water by gavage once daily, 5 days per week for 13 weeks. Groups of 20 mice of each sex received monochloroacetic acid in deionized water by gavage on the same schedule as the rats, but at doses of 0, 25, 50, 100, 150, or 200 mg/kg. Five animals per dose group were designated for interim evaluations after 4 and 8 weeks of chemical administration. Animals were observed twice daily for morbidity and mortality and were given physical examinations weekly (twice during week 1 for rats). Moribund animals were killed and necropsied. Individual animal weights were recorded on a weekly basis and at interim evaluations and at the end of the studies.

Blood and urine were collected from five rats and five mice in each dose group (fewer high-dose rats and mice in the two highest dose groups due to mortality) at weeks 4 and 8 and from all surviving animals at the end of the studies. The parameters measured are listed in Table 1.

After 13 weeks, all surviving animals were killed, and a complete necropsy was performed. Organ weights were determined for the liver, right kidney and adrenal gland, brain, heart, thymus, and lungs of all animals and the right testis of all males. Histopathology was performed on all rats and mice dying before the end of the studies; all rats in the control, 60, 90, 120, and 150 mg/kg groups; and all mice in the control and 200 mg/kg groups. The heart, liver, and lungs from rats in the 30 mg/kg group were also examined. Further details are given in Table 1.

2-YEAR STUDIES

Study Design

Groups of 70 rats of each sex were administered 0, 15, or 30 mg/kg monochloroacetic acid in deionized water by gavage once daily, 5 days per week for 104 weeks. The dose volume was 5 mL/kg. Ten rats per dose group were designated for interim evaluation (necropsy, organ weights, and histopathology) after 6 and 15 months of chemical administration. However, because of early deaths only seven rats per dose group were killed at 15 months. Groups of 60 mice of each sex were given 0, 50, or 100 mg/kg monochloroacetic acid in deionized water by gavage at a dose volume of 10 mL/kg on the same schedule.

Source and Specification of Animals

The male and female F344/N rats and B6C3F$_1$ mice used in the 2-year studies were obtained from Charles River Breeding Laboratories. Rats and mice were shipped to the study laboratory at 4 to 6 weeks of age and were quarantined for 14 to 15 days. During this time, animals were checked daily. To assess the health status of the animals, five rats and five mice per sex were sacrificed for gross examination and determination of pathogen burden. Rats were 6 to 7 weeks old and mice were 7 to 8 weeks old when placed on study. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Rats were housed five per cage. Mice were initially housed five per cage, but any mouse exhibiting poor health, life-threatening tumors or lesions, or dominant aggressive behavior was removed and individually housed for the remainder of the studies. On October 20, 1983, 14 months after study initiation, all male mice were placed in individual cages and remained individually housed until the end of the study. Cages were rotated once a week from top to bottom within a rack and cage racks were moved clockwise to a new location once every 2 weeks. Feed and water were available *ad libitum*. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily for morbidity and mortality and examined for signs of toxicity every 4 weeks. Individual body weights were recorded prior to the initiation of dosing, once per week for the first 13 weeks of the studies, and then once per month through month 21, after which

weights were recorded every 2 weeks. Mean body weights were calculated for each group.

Rats were killed for interim evaluation after 6 months of dosing (10 rats per dose group) and 15 months of dosing (7 rats per dose group). Body weight, organ weights, hematology and clinical chemistry indices (15-month evaluation only), and gross and microscopic pathology were evaluated at these times. Further details of the interim evaluations are given in Table 1.

Animals found moribund and those surviving to the end of the studies were killed. All animals, including those found dead, were necropsied. During necropsy all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin and routinely processed for microscopic examination (embedded in paraffin, sectioned at 4 to 5 μm, and stained with hematoxylin and eosin). A complete histopathologic evaluation inclusive of gross lesions was performed on each animal. Tissues examined microscopically are listed in Table 1.

Upon completion of the microscopic evaluation by the laboratory pathologist, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated. All tissues with a diagnosis of neoplasia, all kidneys from male rats, all uteri from female rats, all noses and forestomachs from male and female mice, and all tissues from a randomly selected 10% of the control and high-dose animals were reevaluated microscopically by the quality assessment pathologists.

The quality assessment reports and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed selected tissues microscopically, including those for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions in the nose and forestomach and neoplasms, including examples of differences in diagnosis between the study pathologist and reviewing pathologist, were selected by the chair for review by the PWG. The PWG consisted of the study pathologist, the quality assessment pathologist, and other pathologists experienced in rodent toxicologic pathology. The group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the Cox's method (1972) 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

Tables A1, B1, C1, and D1 in the appendixes to this report present the incidence of neoplastic lesions in male and female rats and mice. Tables A4, B5, C5, and D5 summarize the incidence of nonneoplastic lesions in male and female rats and mice. The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions had multiple potential sites of occurrence (e.g., lymphomas), the denominators

consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence

The majority of tumors in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

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

Historical Control Data

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

Analysis of Continuous Variables

The nonparametric multiple comparison procedures of Dunn (1964) or Shirley (1977) were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of organ weight data. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICITY

The genetic toxicity of monochloroacetic acid was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium* (strains TA100, TA1535, TA1537, and TA98), sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and trifluorothymidine resistance in mouse L5178Y lymphoma cells. The protocols for these studies and tabular presentations of their findings are given in Appendix E.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Monochloroacetic Acid

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
International Research and Development Corporation, Mattawan, MI	Same as 16-day studies	Same as 16-day studies
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Charles River Breeding Laboratories, Inc., Portage, MI	Same as 16-day studies	Same as 16-day studies
Time Held Before Study		
Rats: 13 days Mice: 15 days	Rats: 13 days Mice: 13 days	Rats: 14 days Mice: 15 days
Average Age When Placed on Study		
Rats: 5-6 weeks Mice: 7-8 weeks	Rats: 6-7 weeks Mice: 7-8 weeks	Rats: 6-7 weeks Mice: 7-8 weeks
Date of First Dose		
Rats: 9 March 1981 Mice: 11 March 1981	Rats: 17 August 1981 Mice: 24 August 1981	Rats: 31 August 1982 Mice: 25 August 1982
Duration of Dosing		
5 days/week for 12 dose days	Rats: 5 days/week for 13 weeks, plus an additional day of dosing in week 14; Mice: 5 days/week for 13 weeks, plus an additional day of dosing in week 14 due to terminal necropsy scheduling.	Rats: 5 days/week for 104 weeks; for 6 and 15 months for interim evaluation animals Mice: 5 days/week for 104 weeks
Date of Last Dose		
Rats: 24 March 1981 Mice: 26 March 1981	Rats: 16 November 1981 Mice: 23 November 1981	Rats: 23 August 1984 Mice: 16 August 1984
Necropsy Dates		
Rats: 26 March 1981 Mice: 27-28 March 1981	Rats: 16-17 November 1981 Mice: 23-24 November 1981	Rats: 6-month interim: 1 March 1983; 15-month interim: 29 November 1983; 2-year: 28-31 August 1984 Mice: 22-24 August 1984
Average Age at Necropsy		
Rats: 8 weeks Mice: 9-10 weeks	Rats: 17-18 weeks Mice: 21-22 weeks	Rats: 111-112 weeks Mice: 111-112 weeks

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Monochloroacetic Acid
(continued)

16-Day Studies	13-Week Studies	2-Year Studies
Size of Study Groups		
5 males and 5 females per species	20 rats and 20 mice per dose group; 5 animals per dose group were scheduled for interim evaluation at 4 and 8 weeks	Rats: 53 rats per dose group; an additional 10 rats per dose group for 6-month interim evaluation and 7 rats per dose group for 15-month interim evaluation Mice: 60 animals per dose group
Method of Animal Distribution		
A computerized random number generator randomly selected the animals for use. A computerized sort produced a listing of the animals by ascending body weight per sex. Blocks were arranged by weight, and the animals were then assigned to groups by sets of random numbers.	Same as 16-day studies	Same as 16-day studies
Animals per Cage		
Rats: 5 Mice: 5	Rats: 5 Mice: 5	Rats: 5 Mice: 5 until 20 October 1983 (14 months after study initiation), after which all males were housed individually
Method of Animal Identification		
Rats: Ear tag Mice: Toe clip	Same as 16-day studies Same as 16-day studies	Same as 16-day studies Same as 16-day studies
Feed		
NIH-07 open formula mash diet (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 16-day studies (animals used for clinical chemistry tests were fasted overnight prior to evaluation)	Same as 16-day studies
Maximum Storage Time for Feed		
120 days after milling	Same as 16-day studies	Same as 16-day studies
Feeders		
Stainless steel, changed weekly	Same as 16-day studies	Same as 16-day studies
Water		
Automatic watering system Edstrom Industries, Inc., Waterford, WI	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Monochloroacetic Acid
(continued)

16-Day Studies	13-Week Studies	2-Year Studies
Cages		
Polycarbonate with Edstrom grommets (Hazleton System Inc., Aberdeen, MD), changed twice weekly for rats and group-housed mice, changed weekly for individually housed mice	Same as 16-day studies Animals used for blood and urine tests on weeks 4, 8, and 13 were transferred to metabolism cages the day before collection.	Same as 16-day studies
Bedding		
BetaChips (Hardwood Laboratory Bedding, Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as 16-day studies	Same as 16-day studies
Cage Filters		
Reemay spun-bonded polyester (Snow Filtration, Cincinnati, OH), changed weekly	Same as 16-day studies, changed biweekly	Same as 16-day studies, changed biweekly
Racks		
Stainless steel, changed weekly	Same as 16-day studies, changed biweekly	Same as 16-day studies, changed biweekly
Animal Room Environment		
Rats: Average temperature: 75.2° F Average humidity: 35.1% Light: fluorescent, 12 hours/day Room air flow: 6-12 changes/hour	Rats: Average temperature: 74.2° F Average humidity: 38.9% Light: fluorescent, 12 hours/day Room air flow: 10-12 changes/hour	Rats: Average temperature: 73 ± 1.6° F Average humidity: 51 ± 15.8% Light: fluorescent, 12 hours/day Room air flow: 10-12 changes/hour
Mice: Average temperature: 75.2° F; Average humidity: 35.4%; Light: fluorescent, 12 hours/day Room air flow: 6-12 changes/hour	Mice: Average temperature: 75.4° F; Average humidity: 51.4%; Light: fluorescent, 12 hours/day Room air flow: 6-12 changes/hour	Mice: Average temperature: 73 ± 1.7° F; Average humidity: 51 ± 15.8%; Light: fluorescent, 12 hours/day Room air flow: 6-12 changes/hour
Doses		
Rats: 0, 7.5, 15, 30, 60, or 120 mg/kg in deionized water administered by gavage Mice: 0, 15, 30, 60, 120, or 240 mg/kg for males and 0, 30, 60, 120, 240, or 480 mg/kg for females; in deionized water administered by gavage	Rats: 0, 30, 60, 90, 120, or 150 mg/kg in deionized water administered by gavage Mice: 0, 25, 50, 100, 150, or 200 mg/kg in deionized water administered by gavage	Rats: 0, 15, or 30 mg/kg in deionized water administered by gavage Mice: 0, 50, or 100 mg/kg in deionized water administered by gavage
Storage Conditions for Dosing Solutions		
Room temperature in the dark	Room temperature in the dark	Room temperature in the dark
Maximum Storage Time for Dosing Solutions		
2 weeks	2 weeks	3 weeks

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Monochloroacetic Acid
(continued)

16-Day Studies	13-Week Studies	2-Year Studies
Type and Frequency of Observation		
Twice daily for morbidity and mortality. Observed for signs of toxicity 0.5, 1, 2, 3, and 4 hours post dose on the first 2 days and once daily (except on weekends) for the remainder of the studies. Body weights recorded prior to initiation of dosing, on days 7 and 14, and at study termination.	Twice daily for morbidity and mortality. Observed for signs of toxicity and palpated for masses 2 times during week 1 and weekly thereafter for rats and weekly, 2 or 4 hours post dose for mice. Body weights recorded at study initiation, on the last day of each study week, prior to the interim kills, and at study termination.	Twice daily for morbidity and mortality. Detailed observations of clinical signs every 4 weeks. Body weights recorded prior to initiation of dosing, weekly for weeks 1-13, then monthly until the last 3 months when weights were recorded biweekly.
Necropsy	**Necropsy**	**Necropsy**
Necropsy on all animals. Weights of brain, heart, right kidney, liver, lungs, and thymus recorded for all animals surviving to the end of the studies.	Necropsy on all animals not killed at 4 or 8 weeks for evaluation of hematologic and clinical chemistry parameters. Organ weights of brain, heart, liver (with gallbladder for mice), lungs, right kidney and adrenal gland, right testis, and thymus were recorded for all animals surviving until the end of the studies.	Necropsy on all animals. Organ weights recorded for rats at 6-month and 15-month interim evaluations: brain, heart, right kidney, and liver (15-month only). Sections of heart tissue were examined microscopically for all rats at the 6-month interim evaluation.
Histopathology	**Histopathology**	**Histopathology**
Rats: complete histopathologic examination of males and females receiving 120 mg/kg. Mice: complete histopathologic examination of the 240 mg/kg dose group; liver, stomach and/or lungs from all lower dose groups. Tissues examined microscopically: adrenal gland, brain, colon, esophagus, gallbladder (mice), heart and aorta, jejunum, kidney, liver, lungs and bronchi, lymph nodes (mandibular and mesenteric), nasal cavity and turbinates, mammary gland, ovary, pancreas, parathyroid gland (rats), pituitary gland, prostate gland (rats), salivary gland, spinal cord, spleen, sternum with marrow, stomach, testis with epididymis, seminal vesicle, and scrotal sac (rats), thymus, thyroid gland, trachea, urinary bladder, uterus	Rats: complete histopathologic examination of all animals that died before termination and on all survivors in the control, 60, 90, 120 and 150 mg/kg groups. The heart, lungs and bronchi, and liver were examined for rats in the 30 mg/kg dose group. Mice: complete histopathologic examination of all early death and moribund sacrifice animals and of all survivors in the control and 200 mg/kg groups. Tissues examined included: adrenal gland, aorta, blood smear (mice), brain, cecum, colon, duodenum, esophagus, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidney, liver, lungs and bronchi, lymph node, mammary gland, nose, ovaries, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland (mice), prostate gland, rectum, salivary gland, spinal cord (mice only, if neurological signs were present), spleen, sternum with marrow, stomach, testis, thymus, thyroid gland, trachea, tissue masses (rats), urinary bladder, uterus.	A complete histopathologic examination of all control and high-dose rats at the 15-month interim evaluation; only gross lesions examined microscopically for low-dose rats at the 15-month interim evaluation. Complete histopathologic examination of all rats and mice dying early, killed in a moribund condition, or killed at the end of the studies. In addition to gross lesions and tissue masses with associated lymph nodes, the following tissues were evaluated: adrenal gland, bone and marrow (femur), brain, cecum, clitoral or preputial gland (rats), colon, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidney, liver, lungs and mainstem bronchi, lymph node (mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, rectum, salivary gland, skin, spleen, stomach, testis with epididymis, thymus, thyroid gland, trachea, urinary bladder, uterus.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Monochloroacetic Acid
(continued)

16-Day Studies	13-Week Studies	2-Year Studies
Clinical Pathology None required	**Clinical Pathology** Hematology, clinical chemistry, and urinalysis tests on blood and urine collected from 5 rats and 5 mice per dose group at weeks 4 and 8, and from all surviving animals at the end of the studies. Bone marrow smears were obtained from rats and mice after 4, 8, and 13 weeks of study. ***Hematology:*** erythrocyte count, leukocyte count and differential, hematocrit, hemoglobin, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, and methemoglobin. ***Clinical chemistry:*** electrolytes; sodium, potassium, calcium, chloride (rats), phosphorus (rats), blood urea nitrogen, creatinine (rats), total bilirubin (rats), aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total protein, albumin, albumin-globulin ratio, cholinesterase, ornithine carbamyl transferase (rats), sorbitol dehydrogenase, triiodothyronine, and thyroxin. ***Urinalysis:*** color, appearance, specific gravity, pH, protein, glucose, occult blood, nitrites, urobilinogen, ketones, and bilirubin.	**Clinical Pathology** Hematology and clinical chemistry tests on blood collected from 7 rats per dose group at the 15-month interim evaluaion. ***Hematology:*** leukocyte count and differential, erythrocyte count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration ***Clinical chemistry:*** alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, hydroxybutyrate dehydrogenase, total protein, and albumin.

RESULTS

RATS

16-Day Studies

One high-dose male died on the third day of dosing; there were no other deaths. The final mean body weights of dosed and control female rats were similar. Male survivors given 120 mg/kg gained 13% less body weight than did controls. Survival and mean body weights are shown in Table 2.

The high-dose rat that died exhibited increased lacrimation, prostration, bradypnea, decreased limb tone, ataxia, and an impaired grasping reflex within 4 hours after dosing. Lacrimation was also observed in other dosed rats, including males receiving 60 or 120 mg/kg and females receiving 15 to 120 mg/kg. Porphyrin staining around the nose was seen on day 2 in one female and in one of the surviving males receiving 120 mg/kg, and a clear nasal discharge was noted on days 12 to 14 in dosed rats of each sex. There were no clinical findings in any of the control animals.

Brain, heart, right kidney, liver, lung, and thymus weights were obtained for all animals that survived until the end of the studies (Appendix F, Table F1a). No change in any organ weight was considered biologically significant.

All animals were examined for gross lesions at necropsy. Histopathology was performed on all high-dose rats. No gross or histopathologic lesions attributable to monochloroacetic acid were observed.

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Studies of Monochloroacetic Acid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	115 ± 6	179 ± 5	64 ± 2	-
7.5	5/5	112 ± 3	175 ± 2	63 ± 1	97
15	5/5	112 ± 4	171 ± 5	59 ± 2	95
30	5/5	111 ± 3	174 ± 4	63 ± 2	97
60	5/5	113 ± 3	175 ± 5	62 ± 2	97
120	4/5[c]	109 ± 2	165 ± 8	56 ± 6	92
Female					
0	5/5	103 ± 4	134 ± 4	31 ± 2	-
7.5	5/5	105 ± 4	136 ± 5	31 ± 2	102
15	5/5	103 ± 3	136 ± 3	33 ± 2	102
30	5/5	104 ± 3	136 ± 3	32 ± 1	102
60	5/5	103 ± 4	135 ± 4	32 ± 1	101
120	5/5	102 ± 3	133 ± 3	31 ± 2	99

[a] Number surviving/number initially in group
[b] Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test.
[c] Day of death: 3

13-Week Studies

Survival and mean body weight information is presented in Table 3. All rats receiving 120 or 150 mg/kg monochloroacetic acid, and all but one receiving 90 mg/kg, died before the end of the studies. Other deaths included two male rats and one female rat receiving 60 mg/kg and one female rat receiving 30 mg/kg monochloroacetic acid. The mean body weights of dosed animals that survived to the end of the studies were similar to those of controls.

Findings consistent with sialodacryoadenitis were noted in dosed and control rats. Serological titers to rat corona virus/sialodacryoadenitis virus were detected in blood from selected rats, and swelling in the ventral cervical region and chronic inflammation of the salivary glands were observed in dosed and control rats. The swelling in the ventral cervical region was likely due to edema and enlargement of the salivary glands and lymph nodes associated with the active phase of the inflammation.

Right adrenal gland, brain, heart, right kidney, liver, lung, right testis, and thymus weights were obtained for all rats that survived until the end of the studies. Absolute and relative heart weights of males and females receiving 60 mg/kg monochloroacetic acid were significantly lower than control values; relative heart weight was also decreased in females receiving 30 mg/kg (Appendix F, Tables F2a and F2b). Relative liver weights of males and females that received 60 mg/kg were significantly greater than the control values, but absolute liver weights were significantly increased only in males. Relative, but not absolute, kidney weights were increased in males receiving 60 mg/kg monochloroacetic acid. These findings are relevant in view of the compound-related changes in clinical chemistry parameters and histopathology. Other changes in organ weights were not considered biologically significant.

A significant, dose-related increase in blood urea nitrogen (BUN) occurred in male rats receiving 90 to 150 mg/kg and in female rats receiving 60 to 150 mg/kg monochloroacetic acid (Appendix G, Table G1). Rats in the lower dose groups also had higher BUN levels than those of controls, but these were not statistically significant. BUN levels in the rat do not increase as a result of kidney damage unless the damage is very severe. For this reason, the increases in BUN were considered to be due to prerenal causes. Although the exact causes remain uncertain, they may have included dehydration or protein catabolism secondary to chemical-related inanition. Significant dose-related increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed in male and female rats receiving 60, 120, or 150 mg/kg monochloroacetic acid; the increases in AST activity were evident after 4 weeks of chemical administration. This trend remained significant after 8 weeks for both AST and ALT in males and for ALT in females, although the increase was not significant at all dose levels. The increases in ALT were consistent with mild hepatocellular damage. The increases in AST may have reflected hepatocellular or cardiac muscle damage.

In a separate study female F344/N rats given a single 150 mg/kg dose of monochloroacetic acid showed a 33% to 44% decrease in heart mitochondrial aconitase activity. No aconitase inhibition occurred in the mitochondrial fraction of livers obtained from these animals (Appendix K). Aconitase is a key Krebs cycle enzyme, and its inhibition may have led to development of cardiomyopathy and the death of rats at the three highest dose levels.

Cholinesterase levels were significantly lower than those of controls in male rats receiving 90 mg/kg monochloroacetic acid for 8 weeks and in male rats receiving 30 or 60 mg/kg for 13 weeks (Table G1). Cholinesterase levels were also significantly lower than controls in all treated groups of female rats after 4 and 8 weeks of compound administration, and in the 60 mg/kg group after 13 weeks of treatment. The reason for these decreases in cholinesterase levels was uncertain, but because the cholinesterase measured in the assay is produced by the liver, the decreased levels may have been a reflection of hepatic toxicity.

Levels of thyroxin (T_4) were significantly higher than those of controls in male rats receiving 90, 120, or 150 mg/kg monochloroacetic acid for 4 weeks, and in males receiving 90 mg/kg for 8 weeks. There were no significant changes in triiodothyronine (T_3) levels. The cause of the changes in T_4 levels was unclear, but it may have been related to liver toxicity. By increasing production of thyroid binding globulin, liver toxicity may have lead to elevated levels of protein-bound T_4 in the blood.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of Monochloroacetic Acid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	140 ± 5	335 ± 9	195 ± 6	
30	10/10	141 ± 5	340 ± 7	199 ± 6	101
60	8/10[c]	138 ± 4	320 ± 8	182 ± 8	96
90	1/10[d]	–[e]	–	–	–
120	0/13[f]	–	–	–	–
150	0/15[g]	–	–	–	–
Female					
0	10/10	112 ± 4	200 ± 5	89 ± 3	
30	9/10[h]	112 ± 3	203 ± 4	91 ± 4	101
60	9/10[i]	111 ± 5	201 ± 6	90 ± 2	100
90	0/10[j]	–	–	–	–
120	0/15[k]	–	–	–	–
150	0/17[l]	–	–	–	–

[a] Number surviving/number initially in group. Does not include interim evaluation animals.
[b] Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test.
[c] Week of death: 1, 11
[d] Week of death: 1, 1, 1, 1, 1, 2, 9, 10, 11
[e] No data reported due to high mortality in this group
[f] Week of death: 1, 1, 1, 2, 2, 4, 5, 6, 6, 6, 8, 8, 8
[g] Week of death: 10 deaths during week 1; additional deaths during weeks 2, 3 (2 deaths), and 5 (2 deaths). All animals in this dose group died during the study except for 5 animals that were killed at 4 weeks for hematology and clinical chemistry determinations.
[h] Week of death: 1; pleuritis was present, indicating that death was probably a gavage accident.
[i] Week of death: 11
[j] Week of death: 1, 1, 1, 2, 2, 2, 4, 7, 8, 13
[k] Week of death: 11 deaths during week 1; additional deaths during weeks 2, 4 (2 deaths), and 5
[l] Week of death: 13 deaths during week 1; 4 deaths during week 2.

Hematocrit, hemoglobin, and erythrocyte counts for male rats that received 150 mg/kg were significantly higher than control values after 4 weeks of compound administration. These increases were consistent with mild dehydration. Segmented neutrophil counts were significantly higher than the control count in male rats in the 90, 120, and 150 mg/kg groups after 4 weeks of treatment. Lymphocyte counts were significantly lower than the control value in male rats that received 30, 60, 90, or 120 mg/kg after 8 weeks of chemical administration. The changes in neutrophil and lymphocyte counts were considered indicative of a stress reaction.

Blood or clear red fluid in the thoracic cavity and congestion of the lungs were observed at necropsy in rats that died during the studies. Mild to severe acute passive congestion was observed in the lungs of rats that died, but not in animals killed at the end of the studies. These lesions were considered to be secondary to myocardial failure induced by the chemical and were consistent with the antemortem finding of dyspnea.

Chemical-related degenerative and inflammatory changes (cardiomyopathy) were observed microscopically in the hearts of male and female rats receiving

60, 90, 120, or 150 mg/kg monochloroacetic acid (Table 4). Acute or subacute cardiomyopathy was observed in rats that died during the studies after receiving 60, 90, 120, or 150 mg/kg and was considered to be the cause of death for these animals. One female given 30 mg/kg that died while on study was free of myocardial changes, but had pleuritis, indicating that death was most likely related to gavage trauma (perforation of the esophagus) (Table 3). Cardiomyopathy was also present among rats given 60 mg/kg that survived to the end of the studies. The compound-related myocardial changes were distinguished from the spontaneous minimal degenerative lesions sometimes observed in rats.

The character and severity of cardiac lesions in the three highest dose groups (90, 120, and 150 mg/kg) varied because time of death and, therefore, duration of treatment varied. The most extensive and severe lesions occurred in rats surviving several days or weeks after treatment was initiated. Lesions occured primarily in the myocardium of the left ventricular wall and interventricular septum. Mild to marked in severity, the lesions noted in these animals consisted of multifocal to diffuse accumulations of mononuclear inflammatory cells (predominantly macrophages) and myofiber degeneration characterized by sarcoplasmic hypereosinophilia, sarcoplasmic vacuolization, and nuclear pyknosis (Plate 1). In more advanced lesions, regenerative myofibers or fibroblasts, or both, with basophilic cytoplasm and elongated vesicular nuclei were also present. Most lesions were located in the interventricular septum and left ventricular wall.

Livers from selected control and treated male and female rats in the 13-week studies were evaluated for peroxisomal proliferation by electron microscopy. There was no apparent increase in the numbers of peroxisomes in rats given monochloroacetic acid.

Dose selection rationale

Based on the mortality of rats given 90 to 150 mg/kg and the cardiomyopathy in rats given 60 to 150 mg/kg monochloroacetic acid in the 13-week studies, the doses selected for the 2-year studies in rats were 15 and 30 mg/kg.

TABLE 4
Incidence of Cardiomyopathy in Rats in the 13-Week Gavage Studies of Monochloroacetic Acid[a]

Diagnosis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Males						
Number Examined	10	10	10	9	13	15
Acute/Subacute Cardiomyopathy	0	0	5*	9**	13**	15**
Females						
Number Examined	10	10	9	10	15	17
Acute/Subacute Cardiomyopathy	0	0	6**	10**	15**	17**

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Incidences represent the consensus of the study pathologist and PWG.

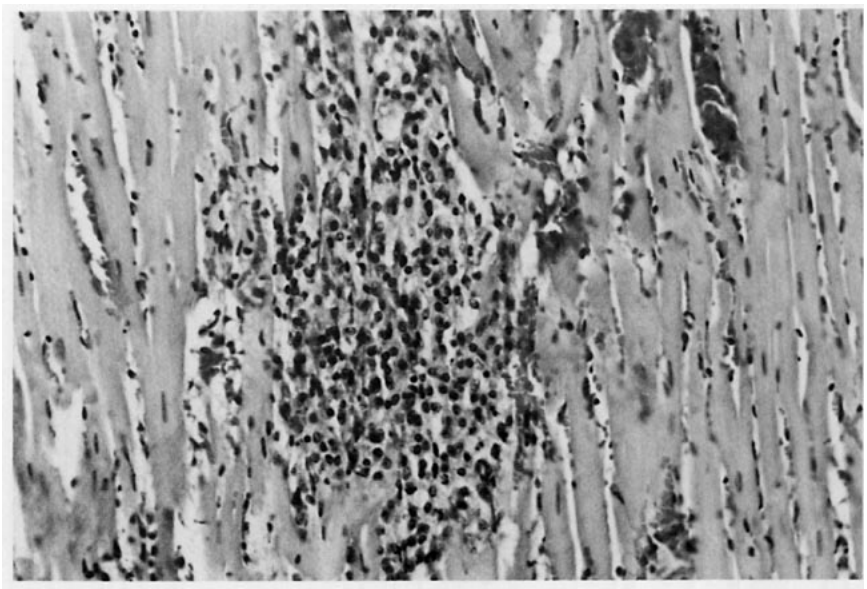


PLATE 1
Cardiomyopathy in the heart of an F344/N rat administered 150 mg/kg monochloroacetic acid for 13 weeks. There has been degeneration and loss of myocardial fibers and accumulation of mononuclear inflammatory cells. Magnification 200×

2-Year Studies

6-Month and 15-Month Interim Evaluations

There were no significant differences in mean body weight at necropsy between dosed and control rats at either evaluation period (Appendix F, Tables F3a and F4a). At the 6-month interim evaluation the relative kidney weights of dosed females and the absolute kidney weights of the high-dose females were significantly less than the controls, while the relative kidney weights of high-dose males were significantly greater than the controls (Tables F3a and F3b). The absolute and relative brain weights of dosed females were significantly less than controls, and relative heart weight of high-dose females was significantly greater than the control. Similar changes in organ weights were not observed in rats at the 15-month interim evaluations (Tables F4a and F4b).

No neoplasms were observed in rats evaluated at 6 months; neoplasms observed in rats evaluated at 15 months are listed in Table 5. None of the neoplastic or nonneoplastic lesions were considered related to the administration of monochloroacetic acid.

Body Weights and Clinical Findings

The mean body weight of high-dose males was approximately 5% less than that of controls during the second year of the study. Mean body weights of all other groups of rats were similar to those of the controls (Tables 6 and 7 and Figure 1). No clinical findings in rats were attributed to the administration of monochloroacetic acid.

TABLE 5
Incidence of Neoplasms in Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
Mammary Gland			
Mixed tumor, benign	0/7[a] (0%)	0/6 (0%)	1/7 (14%)
Pancreas, islets			
Adenoma	0/7 (0%)	0/6 (0%)	1/7 (14%)
Pituitary, pars distalis			
Adenoma	0/7 (0%)	1/6 (17%)	0/7 (0%)
Skin			
Keratoacanthoma	0/7 (0%)	0/6 (0%)	1/7 (14%)
Subcutis, fibroma	0/7 (0%)	0/6 (0%)	1/7 (14%)
Testis			
Interstitial cell adenoma	5/7 (71%)	3/6 (50%)	6/7 (86%)
Female			
Adrenal cortex			
Adenoma	1/7 (14%)	0/4 (0%)	0/7 (0%)
Pituitary, pars distalis			
Adenoma	0/7 (0%)	1/4 (25%)	0/7 (0%)
Uterus			
Stromal polyp	1/7 (14%)	0/4 (0%)	1/7 (14%)

[a] Number of tumor-bearing animals/number of animals examined at site

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid

Weeks on Study	Vehicle Control		15 mg/kg			30 mg/kg		
	Av. Wt. (g)	No. of Survivors[a]	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors[a]	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors[a]
1	195	53	189	97	53	191	98	53
2	237	53	231	97	53	231	98	53
3	263	53	258	98	53	257	98	53
4	280	53	276	99	53	274	98	53
5	292	53	294	101	53	292	100	53
6	304	53	308	101	53	305	100	53
7	323	53	323	100	53	312	97	53
8	335	53	335	100	53	328	98	53
9	347	53	345	100	53	338	98	53
10	356	53	354	100	53	349	98	53
11	365	53	363	100	53	358	98	53
12	372	53	369	99	53	363	98	53
13	380	53	377	99	53	367	97	53
17	409	53	407	100	53	399	98	53
21	424	53	423	100	53	412	97	53
25	438	53	439	100	53	426	97	53
29	461	53	453	98	53	443	96	53
33	472	53	468	99	53	454	96	53
37	480	53	472	98	53	456	95	53
41	487	53	478	98	52	468	96	53
45	484	52	478	99	52	462	96	53
49	469	52	460	98	52	455	97	51
54	466	51	462	99	51	448	96	47
57	472	51	467	99	51	462	98	47
61	476	51	470	99	50	457	96	46
65	482	49	481	100	48	464	96	45
70	484	49	482	100	48	460	95	43
73	484	48	487	101	48	459	95	41
77	481	46	488	102	48	467	97	35
81	475	46	490	103	45	467	98	32
85	486	42	485	100	43	461	95	31
89	486	41	475	98	40	451	93	31
92	488	39	465	95	37	455	93	28
93	481	39	475	99	33	453	94	26
95	475	38	463	98	33	447	94	24
97	468	37	463	99	32	437	93	21
99	461	33	444	96	30	425	92	19
101	456	32	444	98	27	421	92	18
103	449	29	426	95	24	415	92	16
Terminal sacrifice		27			21			16
Mean for weeks								
1-13	311		309	99		305	98	
14-52	458		453	99		442	97	
53-103	475		469	99		450	95	

[a] Does not include interim evaluation animals

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid

Weeks on Study	Vehicle Control		15 mg/kg			30 mg/kg		
	Av. Wt. (g)	No. of Survivors[a]	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors[a]	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors[a]
1	137	53	138	100	53	138	100	53
2	154	53	154	100	52	155	101	53
3	163	53	167	102	52	167	102	53
4	172	53	175	102	52	175	102	53
5	180	53	183	102	52	184	102	53
6	187	53	188	101	52	189	101	53
7	193	53	195	101	52	194	100	53
8	197	53	199	101	52	199	101	53
9	202	53	203	101	52	203	101	53
10	203	53	206	101	52	207	102	53
11	208	53	209	101	52	210	101	53
12	209	53	209	100	52	210	100	53
13	212	53	214	101	52	214	101	53
17	222	53	225	101	52	227	103	53
21	229	53	231	101	52	230	101	53
25	235	53	237	101	52	238	101	53
29	244	53	247	101	52	246	101	53
33	255	52	257	101	52	257	101	53
37	264	52	264	100	50	265	101	51
41	267	52	267	100	50	268	100	49
45	272	52	273	100	49	270	99	48
49	273	52	273	100	49	271	99	46
54	275	51	274	100	49	274	100	45
57	283	51	287	101	49	282	100	45
61	294	51	294	100	49	288	98	45
65	305	51	305	100	48	305	100	45
70	316	51	311	98	48	310	98	44
73	323	51	320	99	46	315	97	43
77	328	49	329	100	45	322	98	42
81	335	47	327	98	43	325	97	41
85	340	47	332	98	39	329	97	38
89	345	46	335	97	36	333	97	35
92	350	44	336	96	33	337	96	35
93	346	44	341	98	28	340	98	34
95	349	43	339	97	26	336	96	33
97	347	41	345	99	23	335	96	33
99	348	37	340	98	22	342	98	30
101	353	37	345	98	20	342	97	29
103	349	37	342	98	20	339	97	28
Terminal sacrifice		37			19			26
Mean for weeks								
1-13	186		188	101		188	101	
14-52	251		253	101		252	100	
53-103	329		324	98		321	98	

[a] Does not include interim evaluation animals

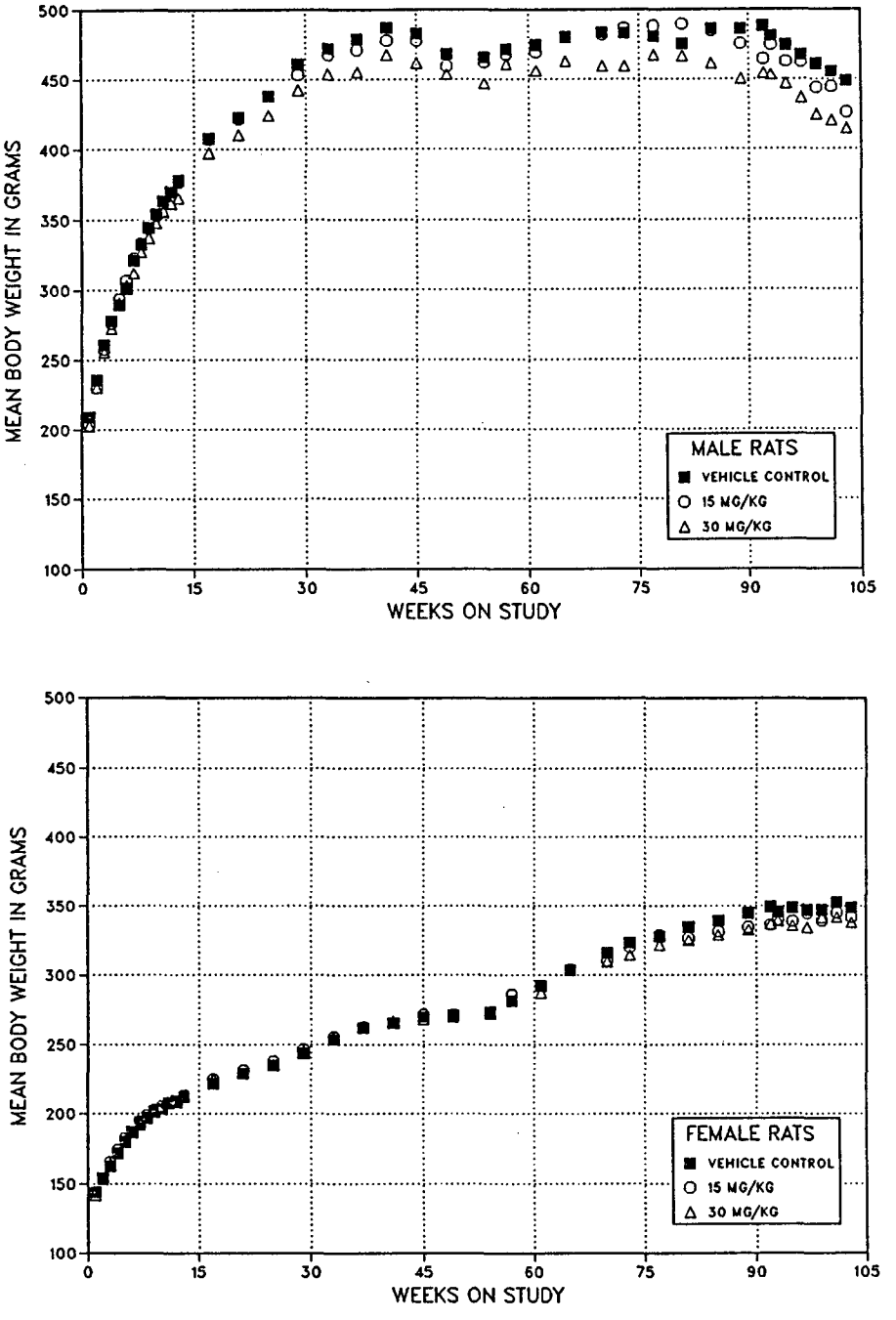


FIGURE 1
Growth Curves for Male and Female Rats Administered Monochloroacetic Acid by Gavage for 2 Years

Survival

Estimates of the probabilities of survival for male and female rats are shown in the Kaplan-Meier curves in Figure 2. Survival of high-dose male and low- and high-dose female rats was significantly lower than that of the controls (Table 8).

The probable causes of natural death or morbidity in male and female rats were determined by gross and microscopic examinations and are given in Table 9. Approximately equal numbers of rats in the control and treated groups died or were found moribund from a variety of neoplastic and non-neoplastic diseases, primarily mononuclear cell leukemia, pituitary gland neoplasms, mammary gland fibroadenomas, and chronic nephropathy.

In the low-dose female group, the increased number of moribund rats was due to an increased incidence of large mammary gland fibroadenomas; the increase in the number of natural deaths was due to an increased incidence of large pituitary gland adenomas.

The decreased survival in treated groups can be attributed to an increase in the number of natural deaths, and, to a lesser extent, to the number of animals moribund due to undetermined causes (male: control, 1/53; low dose, 4/53; high dose, 12/53; female: control, 0/53; low dose, 4/53; high dose, 12/53).

TABLE 8
Survival of Rats in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
Animals initially in study	70	70	70
Natural deaths	8	11	20
Moribund	17	21	15
Accidental deaths[a]	1	0	2
Interim evaluations[a]			
6 month	10	10	10
15 month	7	7	7
Animals surviving to study termination	27	21	16
Percent survival at end of study[b]	53	40	32
Mean survival days[c]	577	570	528
Survival analysis[d]	P=0.011	P=0.287	P=0.015
Female			
Animals initially in study	70	70	70
Natural deaths	2	11	13
Moribund	14	21	13
Accidental deaths[a]	0	2	1
Interim evaluations[a]			
6 month	10	10	10
15 month	7	7	7
Animals surviving to study termination	37	19	26[e]
Percent survival at end of study[b]	70	38	51
Mean survival days[c]	591	544	545
Survival analysis[d]	P=0.043	P=0.001	P=0.046

[a] Censored from survival analyses.
[b] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice).
[d] The entry under the "control" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972).
[e] One of these animals was moribund on the last day of the study.

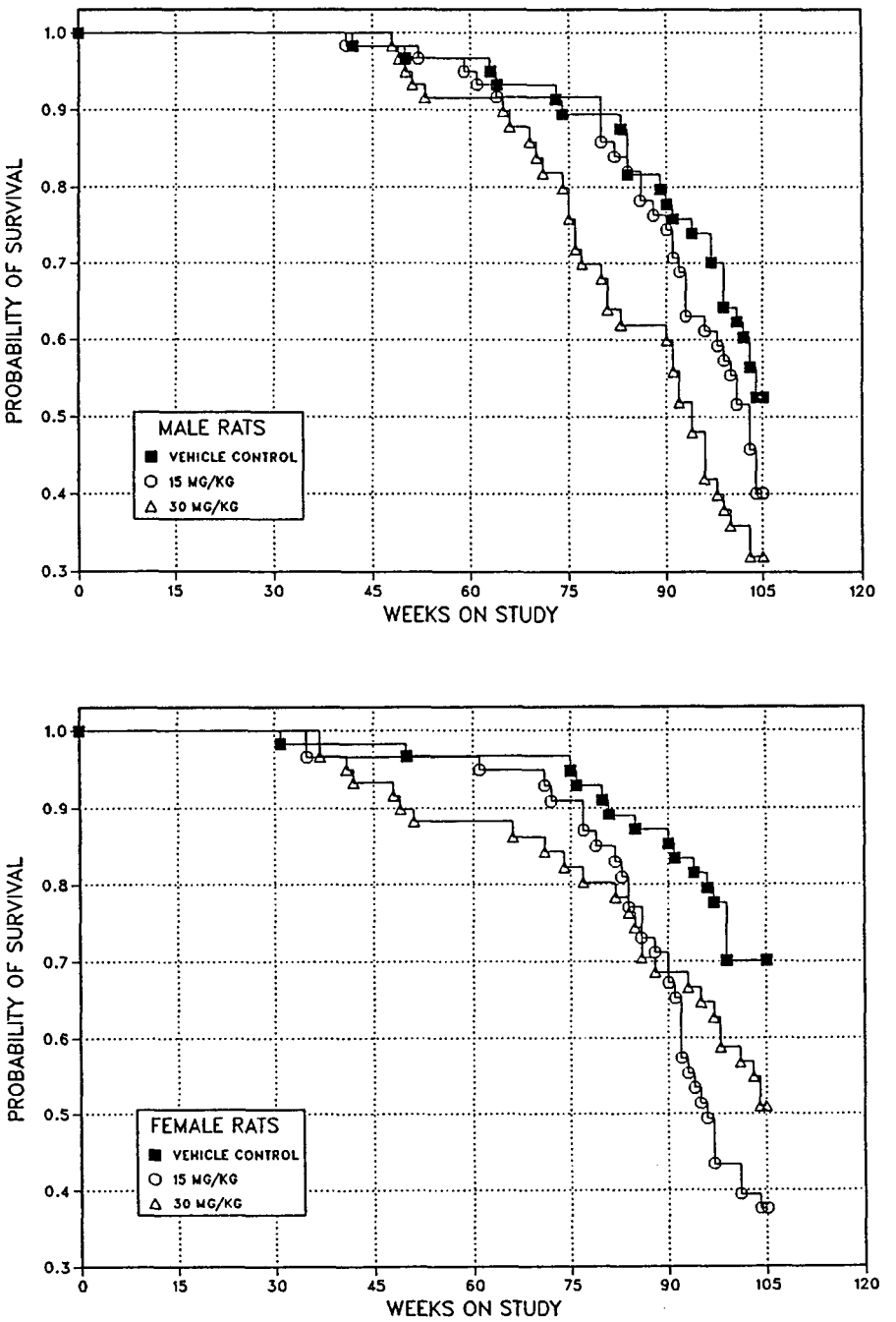


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Monochloroacetic Acid by Gavage for 2 Years

TABLE 9
Causes of Death in Rats in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
Found moribund			
External soft tissue neoplasms	0	1	1
Mononuclear cell leukemia	13	10	9
Miscellaneous neoplasia	2	4	1
Nonneoplastic disease	2	4	2
Undetermined cause	0	2	2
Totals	17	21	15
Found dead			
Mononuclear cell leukemia	2	7	5
Miscellaneous neoplasia	3	2	3
Nonneoplastic disease	2	0	2
Undetermined cause	1	2	10
Totals	8	11	20
Female			
Found moribund			
External soft tissue neoplasms	1	6	1
Mononuclear cell leukemia	9	8	8
Miscellaneous neoplasia	3	5	3
Nonneoplastic disease	1	2	0
Undetermined cause	0	0	1
Totals	14	21	13
Found dead			
Mononuclear cell leukemia	1	2	0
Miscellaneous neoplasia	1	5	2
Nonneoplastic disease	0	0	0
Undetermined cause	0	4	11
Totals	2	11	13

Most deaths occurred between weeks 40 and 92 of the study for males and between weeks 34 and 102 for the females. No significant gross or microscopic lesions were found in any of these animals, and there were no lesions indicative of gavage trauma.

Pathology and Statistical Analyses of Results

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

Uterine endometrial stromal polyps occurred with a significant positive trend in female rats, and the incidences in the low- and high-dose groups were significantly greater than that in the control groups (Table 10). However, because the incidence in the controls was unusually low, and those in the dosed groups were well within the range for historical controls (116/562 or 20.6%, range 10%-38%), it is unlikely that the increase in the incidence of endometrial stromal polyps was related to monochloroacetic acid administration.

In dosed rats, there were marginally decreased incidences of several common neoplasms, including pheochromocytoma of the adrenal medulla, neoplasms of the thyroid C-cells, and mononuclear cell leukemia in males and adenoma of the pituitary pars distalis in males and females (Appendixes A3 and B3). The incidences in the dosed groups were not significantly different from those in controls by the appropriate survival-adjusted analyses. The decreases, therefore, were considered to be the result of decreased survival.

TABLE 10
Incidence of Lesions of the Uterus in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
15-Month Interim Evaluation			
Stromal Polyp[a]			
Overall rates[b]	1/7 (14%)	0/4 (0%)	1/7 (14%)
2-Year Study			
Stromal Polyp			
Overall rates[b]	1/53 (2%)	7/53 (13%)	9/53 (17%)
Adjusted rates[c]	2.7%	26.6%	26.8%
Terminal rates[d]	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	729 (T)	504	512
Logistic regression tests[e]	P=0.006	P=0.024	P=0.006
Stromal Sarcoma[f]			
Overall rates[b]	1/53 (2%)	0/53 (0%)	0/53 (0%)
Stromal Polyp or Stromal Sarcoma[g]			
Overall rates	2/53 (4%)	7/53 (13%)	9/53 (17%)
Adjusted rates	5.1%	26.6%	26.8%
Terminal rates	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	691	504	512
Logistic regression tests	P=0.015	P=0.062	P=0.018
15-Month Interim Evaluation and 2-Year Study			
Stromal Polyp or Stromal Sarcoma[g]			
Overall rates	3/60 (5%)	7/57 (12%)	10/60 (17%)
Adjusted rates	6.8%	26.6%	28.3%
15-month evaluation	1/7 (14%)	0/4 (0%)	1/7 (14%)
Terminal rates	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	456 (I)	504	456 (I)
Logistic regression tests	P=0.022	P=0.125	P=0.031

(T) Terminal incidence
[a] 2-year historical incidence for control groups receiving water vehicle in NTP studies (mean ± standard deviation): 116/562 (20.6% ± 7.6%); range 10%-38%
[b] Incidence expressed as number of animals with lesion/total number of animals necropsied
[c] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal.
[f] 2-year historical incidence for control groups receiving water vehicle in NTP studies: 2/562 (0.4% ± 0.8%); range 0%-2%
[g] 2-year historical incidence for control groups receiving water vehicle in NTP studies: 118/562 (21.0% ± 7.9%); range 10%-38%

MICE

16-Day Studies

All females receiving 480 mg/kg and all male and female mice receiving 240 mg/kg died within two days. One male mouse in the 15 mg/kg group died due to gavage accident (Table 11).

The final mean body weights of male and female mice receiving monochloroacetic acid were not significantly different from those of controls; however, all groups of dosed mice gained more weight than the control animals.

Clinical findings in the mice that died included lacrimation, ataxia, hypoactivity, bradypnea, bradycardia, hypothermia, prostration, piloerection, decreased limb tone, and impaired grasping reflex. Lacrimation was also observed in females receiving 120 mg/kg monochloroacetic acid.

The organ weights and organ-weight-to-body-weight ratios for male and female mice are shown in Appendix F, Tables F5a and F5b. There were no biologically significant changes in these parameters in mice receiving monochloroacetic acid.

No gross or histopathologic lesions were attributed to monochloroacetic acid.

TABLE 11
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of Monochloroacetic Acid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.6 ± 1.1	23.8 ± 1.1	0.2 ± 0.2	
15	4/5[c]	21.0 ± 1.3	22.3 ± 1.3	1.3 ± 0.3*	93
30	5/5	22.8 ± 0.9	24.4 ± 0.9	1.6 ± 0.2**	103
60	5/5	22.2 ± 0.8	24.0 ± 0.9	1.8 ± 0.4**	101
120	5/5	23.6 ± 1.0	26.4 ± 1.0	2.8 ± 0.4**	111
240	0/5[d]	-[e]	-	-	-
Female					
0	5/5	20.2 ± 0.7	19.8 ± 0.4	-0.4 ± 0.5	
30	5/5	19.4 ± 0.4	19.8 ± 0.6	0.4 ± 0.2	100
60	5/5	18.6 ± 0.5	20.0 ± 0.7	1.4 ± 0.2**	101
120	5/5	19.2 ± 0.5	20.4 ± 0.4	1.2 ± 0.4*	103
240	0/5[f]	-	-	-	-
480	0/5[g]	-	-	-	-

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Number surviving/number initially in group
[b] Mean ± standard error
[c] Day of death: 2 (gavage error)
[d] Day of death: 1, 2, 2, 2, 2
[e] No data reported due to 100% mortality in this group
[f] Day of death: 1, 1, 2, 2, 2
[g] Day of death: 1, 1, 1, 1, 2

13-Week Studies

Survival and body weight information for animals not used in the interim evaluations is presented in Table 12. All males and two females given 200 mg/kg died or were killed moribund before the end of the studies; all but two of these deaths occurred during the first week of chemical administration. Two males given 200 mg/kg and one female in the 100 mg/kg group died from gavage trauma; two control males died of unknown causes. With the exception of females receiving 200 mg/kg monochloroacetic acid, the mean body weights of dosed mice were similar to those of controls. The final mean body weight and the mean weight gain for the high-dose females were significantly less than controls. No clinical findings were attributed to monochloroacetic acid.

Group mean organ weights and organ-weight-to-body-weight ratios are shown in Appendix F, Tables F6a and F6b. Absolute and relative liver weights were significantly increased in female mice that received 200 mg/kg monochloroacetic acid.

Cholinesterase levels were significantly decreased in female mice receiving 150 or 200 mg/kg monochloroacetic acid for 8 or 13 weeks (Appendix G, Table G3). The significance of these decreases was unclear, but because cholinesterase is produced by the liver, the decreases may have been a result of liver toxicity.

Minimal to marked hepatocellular cytoplasmic vacuolation was present in the livers of some mice that died during the studies and was characterized by the presence of multiple small- to medium-sized clear vacuoles with distinct borders (compatible with lipid accumulation). In less severely affected livers, the vacuoles generally were small and occurred either diffusely or as a generalized change affecting centrilobular, periportal, or midzonal areas. In severely affected livers the change was diffuse, and vacuoles were larger, often displacing the hepatocyte nuclei. Among the animals that died during the studies, hepatocellular cytoplasmic vacuolization was observed in five males and one female given 200 mg/kg monochloroacetic acid. These changes

TABLE 12
Survival and Mean Body Weights of Mice in the 13-Week Gavage Studies of Monochloroacetic Acid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	8/10[c]	22.3 ± 0.5	28.9 ± 0.5	6.6 ± 0.3	
25	10/10	22.4 ± 0.4	30.4 ± 0.5	8.0 ± 0.5	105
50	10/10	22.4 ± 0.5	29.2 ± 0.9	6.8 ± 0.8	101
100	10/10	21.8 ± 0.5	29.4 ± 0.6	7.6 ± 0.3	102
150	10/10	21.9 ± 0.5	28.6 ± 0.6	6.7 ± 0.6	99
200	0/12[d]	-[e]	-	-	-
Female					
0	10/10	18.1 ± 0.4	24.2 ± 0.6	6.1 ± 0.4	
25	10/10	18.3 ± 0.3	23.7 ± 0.2	5.4 ± 0.3	98
50	10/10	17.8 ± 0.4	23.4 ± 0.5	5.6 ± 0.2	97
100	9/10[f]	18.6 ± 0.4	24.8 ± 0.2	6.2 ± 0.3	102
150	10/10	17.8 ± 0.3	23.0 ± 0.4	5.2 ± 0.4	95
200	8/10[g]	17.9 ± 0.4	21.9 ± 0.8*	4.0 ± 0.9*	90

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Number surviving/number initially in group. Does not include interim evaluation animals except where noted.
[b] Mean ± standard error
[c] Week of death: 2, 3; cause of death unknown
[d] Week of death: 11 deaths during week 1; 1 death during week 8; 2 deaths were due to gavage error (includes 2 interim evaluation animals).
[e] No data reported due to 100% mortality in this group.
[f] Week of death: 1 (gavage error)
[g] Week of death: 1, 5

were attributed to metabolic derangement occurring in moribund animals rather than directly to monochloroacetic acid. Electron microscopic evaluation of livers from selected treated and control mice revealed no evidence of peroxisome proliferation.

Dose selection rationale

Based on the mortality, body weight changes, and hepatic lesions observed in the 13-week studies, the doses selected for the 2-year studies in mice were 50 and 100 mg/kg.

2-Year Studies

Body Weights and Clinical Findings

Mean body weights of male mice and low-dose females receiving monochloroacetic acid were within 5% of those of the controls throughout the studies (Tables 13 and 14 and Figure 3). During the second year of the study the high-dose female mice consistently weighed 8% to 11% less than the controls. No clinical findings were attributed to monochloroacetic acid.

TABLE 13
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.5	60	23.2	99	60	23.5	100	60
2	24.4	60	24.1	99	57	24.5	100	59
3	25.1	60	24.7	98	57	23.9	95	58
4	25.8	60	25.8	100	57	25.9	100	58
5	26.6	60	26.4	99	57	26.7	100	58
6	26.5	60	26.7	101	57	26.6	100	58
7	27.2	60	27.1	100	57	27.1	100	58
8	27.6	60	27.8	101	57	27.5	100	58
9	28.2	59	28.6	101	57	28.6	101	55
10	28.3	59	28.4	100	55	28.8	102	55
11	28.6	59	28.7	100	55	29.4	103	55
12	29.1	59	29.3	101	55	29.4	101	55
13	30.0	59	30.2	101	55	30.3	101	55
17	30.3	59	30.4	100	55	31.0	102	54
21	31.0	59	31.7	102	53	31.5	102	53
25	32.2	58	31.9	99	53[a]	32.8	102	52
29	32.6	58	32.7	100	53	33.1	102	51
33	32.1	58	32.4	101	53	33.2	103	51
37	33.5	58	33.3	99	53	34.0	102	51
41	33.9	58	33.5	99	53	34.0	100	50
45	33.6	58	33.5	100	53	33.9	101	50
49	34.1	58	33.7	99	53	34.1	100	49
53	34.3	57	34.1	99	53	34.4	100	48
57	33.9	57	33.4	99	53	34.5	102	48
61	33.8	57	33.7	100	53	34.2	101	47
65	33.5	56	33.3	99	52	33.9	101	41
69	33.4	56	33.5	100	52	33.8	101	39
73	33.2	56	33.6	101	52	34.5	104	36
77	32.9	55	32.5	99	52	33.4	102	35
81	33.8	54	33.3	99	50	34.1	101	32
85	33.6	54	33.6	100	48	35.1	105	29
89	34.0	54	33.5	99	47	34.7	102	27
91	33.8	52	33.3	99	47	33.9	100	27
93	33.9	51	33.2	98	46	33.8	100	26
95	32.7	49	33.0	101	45	33.7	103	26
97	34.2	49	33.8	99	42	33.9	99	24
99	33.6	48	33.4	99	41	33.5	100	24
101	33.9	47	33.7	99	41	33.8	100	23
103	33.7	46	33.0	98	39	33.8	100	22
Terminal sacrifice		46			39			21
Mean for weeks								
1-13	27.0		27.0	100		27.1	100	
14-52	32.6		32.6	100		33.1	102	
53-103	33.7		33.4	99		34.1	101	

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

TABLE 14
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.8	60	18.5	98	60	18.6	99	60
2	19.6	60	19.4	99	60	19.7	101	60
3	20.4	60	19.3	95	60	20.3	100	60
4	21.2	60	20.6	97	60	21.0	99	60
5	21.5	60	21.2	99	60	21.4	100	59
6	22.0	60	21.6	98	60	21.6	98	59
7	22.9	60	21.7	95	60	22.5	98	59
8	22.9	60	22.2	97	60	22.5	98	59
9	23.2	60	22.8	98	60	22.8	98	59
10	23.1	60	23.0	100	60	23.1	100	58
11	23.6	60	23.5	100	60	23.4	99	58
12	23.8	60	23.2	98	60	23.2	98	58
13	24.7	60	24.1	98	60	24.0	97	58
17	25.0	60	24.6	98	60	24.4	98	57
21	26.0	60	25.2	97	60	25.2	97	56
25	27.0	59	26.4	98	60	25.5	94	56
29	27.7	59	26.7	96	60	26.5	96	52
33	27.3	59	26.2	96	60	25.7	94	52
37	28.4	59	27.9	98	59	27.2	96	52
41	29.6	59	28.4	96	59	27.3	92	52
45	29.8	59	28.1	94	58	27.5	92	52
49	30.4	59	28.7	94	58	27.8	91	52
53	30.7	59	29.0	95	58	28.2	92	52
57	31.0	59	29.3	95	57	28.2	91	52
61	31.1	59	29.9	96	57	28.6	92	52
65	31.5	59	30.3	96	57	28.4	90	52
69	32.3	58	30.7	95	57	28.8	89	52
73	31.7	58	31.2	98	56	28.9	91	52
77	31.8	56	30.3	95	56	28.4	89	52
81	33.4	56	31.1	93	54	29.7	89	52
85	32.8	56	32.1	98	51	29.4	90	51
89	32.9	56	31.7	96	50	29.8	91	51
91	33.0	53	31.4	95	49	29.9	91	51
93	33.5	53	32.1	96	46	29.7	89	49
95	32.6	52	31.7	97	45	30.0	92	48
97	33.1	50	31.8	96	44	30.5	92	47
99	32.5	47	31.6	97	44	29.9	92	47
101	32.8	47	31.7	97	41	29.9	91	47
103	32.2	44	31.6	98	40	30.4	94	46
Terminal sacrifice		42			40			44
Mean for weeks								
1-13	22.1		21.6	98		21.9	99	
14-52	27.9		26.9	96		26.3	94	
53-103	32.3		31.0	96		29.3	91	

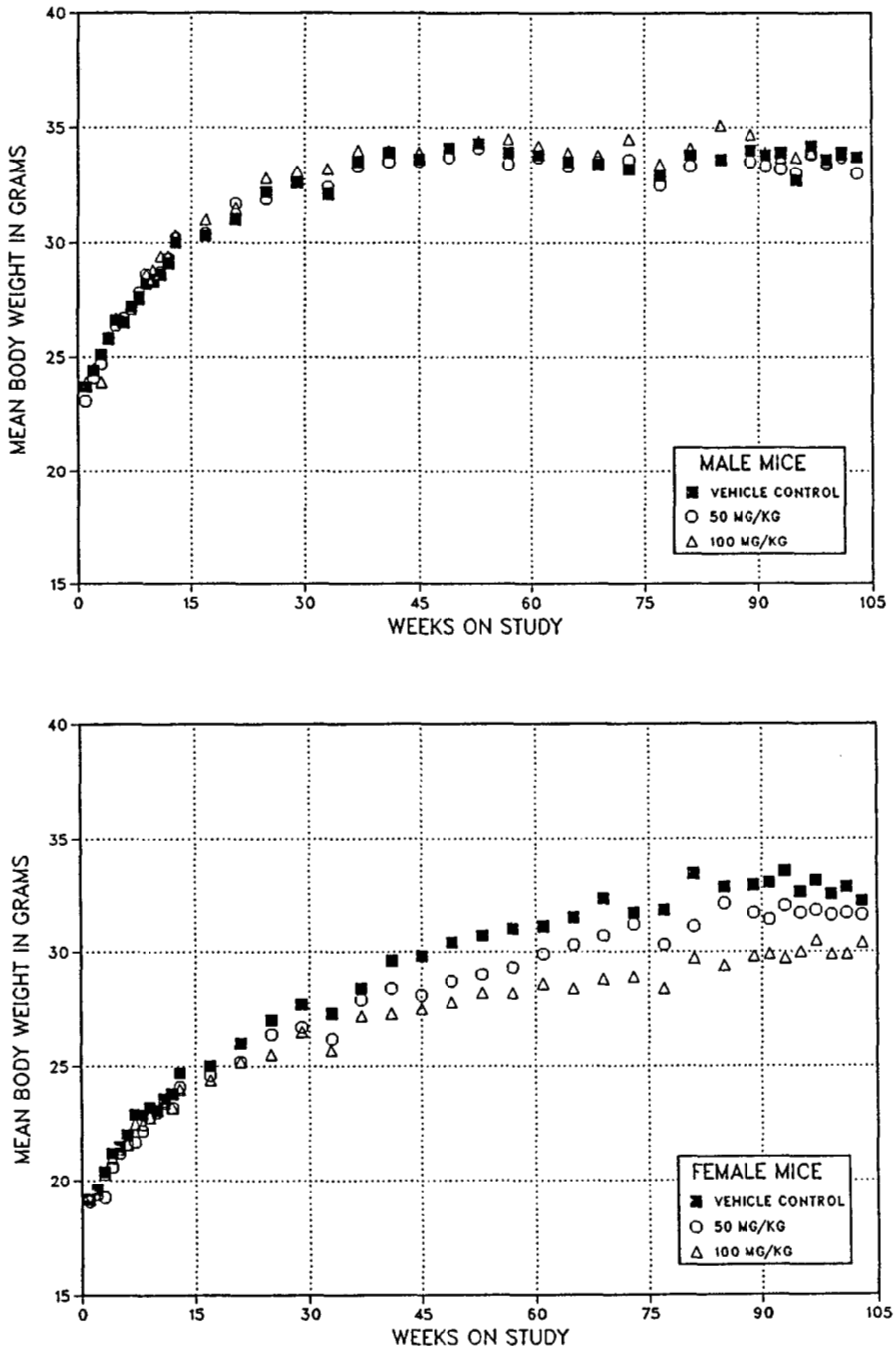


FIGURE 3
Growth Curves for Male and Female Mice Administered Monochloroacetic Acid by Gavage for 2 Years

Survival

Estimates of the probabilities of survival for male and female mice are shown in the Kaplan-Meier curves in Figure 4. Survival of high-dose male mice was significantly lower than that of the control group (Table 15). Survival of low-dose males and low- and high-dose females was similar to that of the controls.

The probable causes of natural death or morbidity in male and female mice were determined by gross and microscopic examinations and are given in Table 16. Approximately equal numbers of mice in control and treated groups died or were found moribund from a variety of neoplastic and nonneoplastic diseases, primarily sarcomas in males and lymphomas in females. The number of natural deaths from miscellaneous neoplasms in high-dose females was slightly fewer than that in the other female groups reflecting the lower number of deaths from lymphoma in this group. Several males in the treated groups died or were moribund from fight wounds (combined incidence: 0/60, 4/60, 7/60). Many of the affected males had lacerations of the prepuce or penis and a number of these animals had ascending urinary tract infections, which were presumably secondary to the preputial and penile lesions. The combined incidence of natural deaths or moribund animals from undetermined cause is as follows: 2/60, 6/60, 12/60. These deaths occurred throughout the study. No significant gross or microscopic lesions were found in any of these animals, and there were no lesions indicative of gavage trauma. The increase in death from undetermined causes may have been due to chemical toxicity.

TABLE 15
Survival of Mice in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	7	11	26
Moribund	5	10	8
Accidental deaths[a]	2	0	5
Animals surviving to study termination	46	39	21
Percent survival at end of study[b]	79	65	38
Mean survival days[c]	683	627	530
Survival analysis[d]	P<0.001	P=0.096	P<0.001
Female			
Animals initially in study	60	60	60
Natural deaths	9	12	9
Moribund	8	8	4
Accidental deaths[a]	1	0	3[e]
Animals surviving to study termination	42[f]	40	44
Percent survival at end of study[b]	71	67	76
Mean survival days[c]	696	680	642
Survival analysis[d]	P=0.780N	P=0.565	P=0.800N

[a] Censored from survival analyses.
[b] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice).
[d] The entry under the "control" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972). Negative trends are indicated by "N".
[e] Only two accidental deaths were censored from survival analyses for high-dose female mice.
[f] One of these animals was found dead on the last day of the studies.

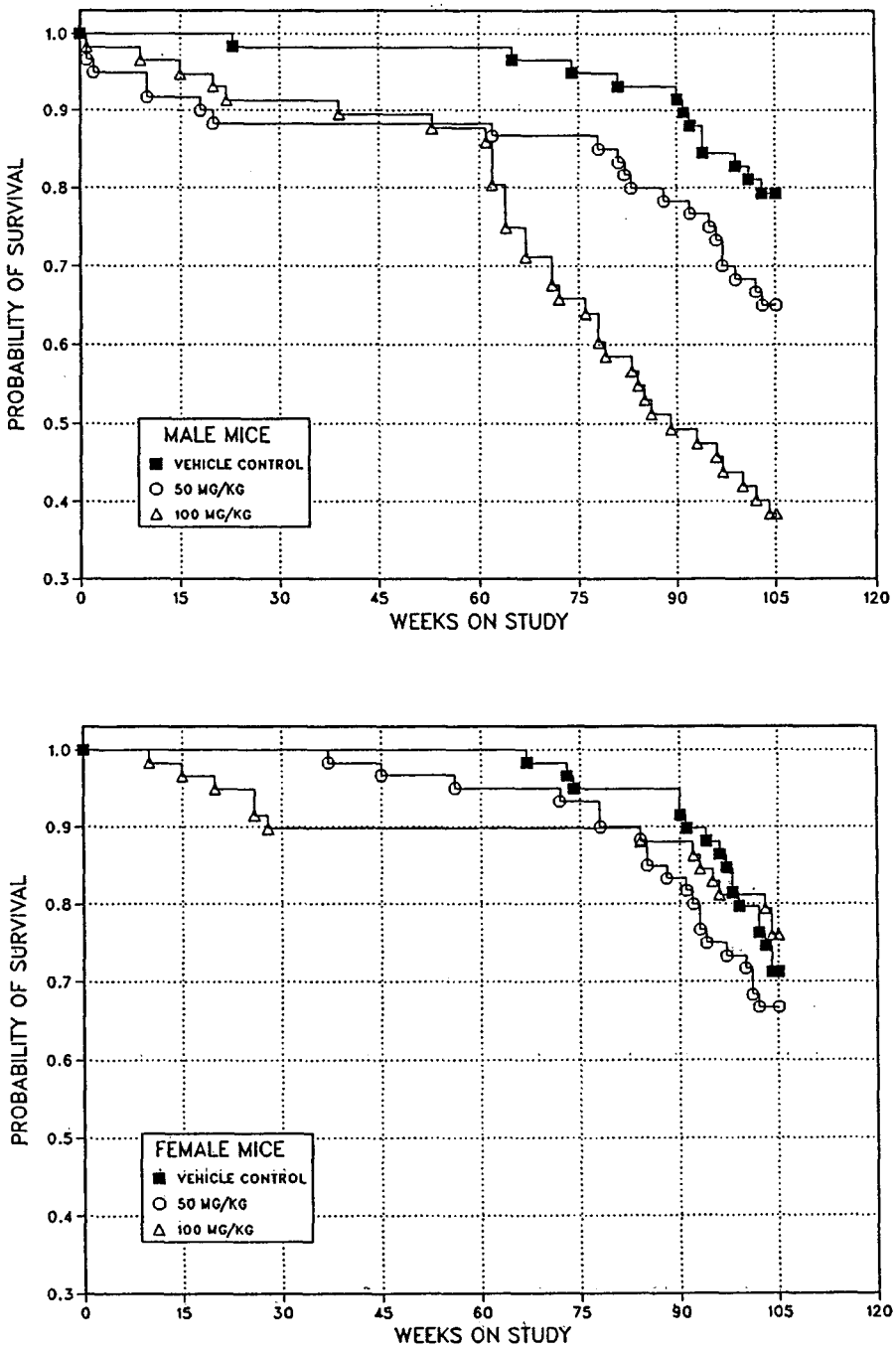


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered Monochloroacetic Acid by Gavage for 2 Years

TABLE 16
Causes of Death in Mice in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Male			
Found moribund			
External soft tissue neoplasms	1	3	1
Fight wounds	0	1	2
Miscellaneous neoplasia	1	3	0
Nonneoplastic disease	2	2	3
Undetermined cause	1	1	2
Totals	5	10	8
Found dead			
Fight wounds	0	3	5
Miscellaneous neoplasia	5	2	7
Nonneoplastic disease	1	1	4
Undetermined cause	1	5	10
Totals	7	11	26
Female			
Found moribund			
External soft tissue neoplasms	1	0	0
Miscellaneous neoplasia	5	6	4
Nonneoplastic disease	1	0	0
Undetermined cause	1	2	0
Totals	8	8	4
Found dead			
Miscellaneous neoplasia	8	10	3
Nonneoplastic disease	0	1	2
Undetermined cause	1	1	4
Totals	9	12	9

Pathology and Statistical Analyses of Results

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

Multiple Organs: There was a dose-related decrease in the incidence of malignant lymphomas (lymphocytic, mixed, and undifferentiated) in female mice (control, 29/60; low-dose, 18/60; high-dose, 13/60). The trend test and pairwise comparison of the high-dose group with the control were significant ($P \leq 0.01$).

Forestomach: Squamous cell papillomas occurred in the forestomachs of two high-dose females; none were seen in control or low-dose females. The incidence of squamous cell papillomas in control female mice from recent NTP water gavage studies is 7/544 (1.3%), with as many as 3/50 (6%) in a given control group. Forestomach squamous cell hyperplasia occurred with a significantly increased incidence in high-dose mice of each sex. The incidence of focal or multifocal squamous hyperplasia of the forestomach was 5/60, 2/60, and 13/60 in males and 5/60, 8/59, and 15/60 in females.

Forestomach squamous cell hyperplasia consisted of single or multiple discrete areas in which some lesions had central erosion, ulcers, or inflammatory cell infiltrates (acute and/or chronic inflammation). Accumulated keratin and increased numbers of cell layers caused thickening and folding of the mucosa.

Nose: Dose-related increases in the incidence of nonneoplastic lesions of the nasal cavity were observed in mice of both sexes, but the increases were more marked in the female groups. The incidence of acute nasal inflammation in high-dose males and low- and high-dose females was significantly greater than that in controls; the incidence in males was 3/60 (5%), 7/59 (12%), 24/60 (40%); the incidence in females was 5/60 (8%); 15/60 (25%); 31/60 (52%). The incidence of metaplasia of the olfactory epithelium was 0/60 (0%), 3/59 (5%), and 2/60 (3%) in males, and 2/60 (3%), 5/60 (8%), and 17/60 (28%) in females. The incidence was significantly greater only in high-dose females. Acute inflammation consisted of mucosa or lamina propria accumulations of neutrophils and/or mononuclear inflammatory cells in varying proportions, with or without inflammatory cells in the nasal cavity. Occasionally, clusters of inflammatory cells (exudate) were seen only in the nasal cavity lumen. Lesions ranged from minimal to mild in severity and were seen most frequently in the antero-ventral regions of the nasal cavity. Foreign material, usually hair shafts, was often seen in the nasal cavity exudate. Generally mild in severity, olfactory epithelial metaplasia was characterized by replacement of the normal olfactory epithelium of the dorso-posterior nasal mucosa by ciliated columnar cells resembling respiratory epithelium. The nasal lesions may have resulted from reflux of gavage solution rather than from a direct toxic effect of monochloroacetic acid.

GENETIC TOXICOLOGY

At concentrations of 10 to 3,333 μg/plate, monochloroacetic acid did not induce mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested with a preincubation protocol in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). In the mouse lymphoma assay, monochloroacetic acid induced trifluorothymidine resistance in L5178Y cells in the absence of S9 at 400 μg/mL and 800 μg/mL, concentrations that caused an acidic pH shift in the cultures (Table E2; McGregor *et al.*, 1987). The responses in the first and third trials were considered positive; the results of the second trial were inconclusive because the highest nontoxic dose achieved was only 250 μg/mL, and the relative total growth (mean, 65%) indicated that higher doses were possible. In cytogenetic tests with Chinese hamster ovary cells, monochloroacetic acid induced sister chromatid exchanges at concentrations of 160 and 500 μg/mL without S9 but not in the presence of S9 (Table E3; Galloway *et al.*, 1987). Monochloroacetic acid did not induce chromosomal aberrations in Chinese hamster ovary cells without S9 (Table E4; Galloway *et al.*, 1987). Small, dose-related increases in chromosomal aberrations were observed in both trials; however, these were not statistically significant. Monochloroacetic acid administered by feed did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Table E5), but when injected it did produce an equivocal response (Table E5).

DISCUSSION AND CONCLUSIONS

Monochloroacetic acid, a colorless crystalline compound, is used as a postemergence contact herbicide and as an intermediate in the synthesis of various dyes and other organic compounds. Haloacetic acids, including monochloroacetic acid, are byproducts of water chlorination. Monochloroacetic acid was nominated by the Environmental Protection Agency for toxicology and carcinogenicity testing because of its large production volume, its presence in drinking water supplies, and the lack of information on its carcinogenic potential. Toxicity and carcinogenicity studies were conducted by administering monochloroacetic acid in water by gavage to groups of F344/N rats and B6C3F$_1$ mice. The gavage route of administration was selected to maximize the dose administered and because the most common route of human exposure to this chemical is the oral route.

The NTP 16-day and 13-week studies of monochloroacetic acid confirm previous findings on the relative toxicity of this compound to rats and mice and provide new information on the organs affected. In the 13-week studies, most deaths occurred in rats given 90 mg/kg or greater monochloroacetic acid and in mice given 200 mg/kg. The reported LD_{50} values are 76 mg/kg in rats (Woodward *et al.*, 1941) and 165 mg/kg (Morrison and Leake, 1941) or 255 mg/kg (Woodward *et al.*, 1941) in mice.

Clonic and tonic convulsions and respiratory depression have been observed in mice given single lethal doses of monochloroacetic acid (Hayes *et al.*, 1973), and in the NTP 16-day studies impaired grasping reflex, decreased limb tone, and ataxia were observed in rats and mice that died. Although these clinical findings suggest an effect on the central nervous system, no microscopic lesions were seen in the brains of rats or mice in the NTP studies. However, Berardi *et al.* (1987) have reported increased front paw rigidity, loss of cerebellar Purkinje cells, and changes in brain microvasculature as demonstrated by microhemorrhages, and increased uptake of ^{14}C-inulin and ^{3}H-dopamine in Swiss-Webster mice given monochloroacetic acid.

In rats administered monochloroacetic acid for 13 weeks, the principal organ affected was the heart. Myocardial degeneration with an associated inflammatory response was observed in rats that died before the end of the studies as well as in rats that survived 13 weeks. The development of these lesions may be attributed to the ability of monochloroacetic acid to inhibit aconitase (a key Krebs cycle enzyme) activity in heart muscle. The increase in serum levels of aspartate aminotransferase (AST) in dosed rats is consistent with this finding, although a tissue source for this enzyme other than the heart cannot be ruled out. Heart muscle is known to contain a high concentration of AST, and elevated serum levels (up to 10 to 15 times normal levels) are seen with cardiac infarction and necrosis (Kachmar and Moss, 1982). No microscopic lesions were observed in the liver, but the significantly increased liver weights and serum alanine aminotransferase levels suggest that the liver is also affected. Significant increases in blood urea nitrogen (BUN) were also observed in dosed rats, but there was no microscopic evidence of kidney damage. Although oxalic acid is a minor (0.1%-0.2%) urinary metabolite of monochloroacetic acid (Yllner, 1971a), formation of oxalate crystals in the renal tubules was not observed and might not occur at the low concentrations of oxalic acid expected. Kidney damage generally does not cause an increase in BUN unless the damage is relatively severe. Thus, the elevation in BUN in this study may be prerenal in origin, perhaps caused by decreased renal perfusion from cardiovascular failure, dehydration, or protein catabolism secondary to debilitation from chemical toxicity.

In contrast to rats, few morphological or functional alterations were observed in mice in the NTP 13-week studies. Increases in liver weight occurred in high-dose females, and hepatocellular cytoplasmic vacuolation consistent with lipid accumulation was seen in mice that died before the end of the studies.

The biochemical mechanisms mediating the acute toxicity and lethality of monochloroacetic acid have not been identified. In studies comparing mono-

chloroacetate with monofluoroacetate and monoiodoacetate in rats, the LD_{50} of monochloroacetate (108 mg/kg) was approximately 20 times that of monofluoroacetate (5 mg/kg) and nearly twice that of monoiodoacetate (60 mg/kg) (Hayes *et al.*, 1973). In rats given an LD_{50} dose, however, the median time to death was shorter in those given monochloroacetate (130 minutes) than in those given monofluoroacetate (310 minutes) or monoiodoacetate (480 minutes). Monochloroacetate also inhibited acetate oxidation *in vitro*, suggesting that monochloroacetate may produce toxic effects through a mechanism similar to that of monofluoroacetate, which produces its toxic effects by inhibiting the citric acid cycle. The fluoroacetate is incorporated into fluoroacetyl coenzyme A, which condenses with oxaloacetate to form fluorocitrate. Fluorocitrate inhibits the enzyme aconitase and inhibits the conversion of citrate to isocitrate. That monochloroacetic acid inhibits aconitase activity in the myocardia of rats suggests that heart failure may be the cause of death in rats receiving high doses of this compound. On the other hand, monochloroacetate was also shown to reduce sulfhydryl concentrations in liver and kidney, in contrast to monofluoroacetate. Thus, the mechanism of toxicity of monochloroacetate may also involve the inhibition of sulfhydryl-containing enzymes.

The doses selected for the NTP 2-year studies in rats were determined from results of the 16-day and 13-week studies. Nearly all rats receiving 90 mg/kg or greater monochloroacetic acid died during the 13-week studies and two males and one female receiving 60 mg/kg died. Myocardial lesions were seen in about half of the rats given 60 mg/kg. Therefore, the doses chosen for the 2-year studies in rats were 30 mg/kg for the high dose and 15 mg/kg for the low dose. In mice, all males and two females receiving 200 mg/kg monochloroacetic acid died during the 13-week studies. For the 2-year studies in mice, the doses chosen were 100 mg/kg and 50 mg/kg.

In the 2-year studies, survival of high-dose male rats and of low- and high-dose female rats was lower than that of controls. Although deaths were caused by a variety of spontaneous neoplasms (primarily mononuclear cell leukemia, pituitary gland tumors, and mammary gland fibroadenomas) and age-related nonneoplastic disease, the reduced survival of the high-dose groups was largely due to animals found moribund or to natural deaths from undetermined cause. There was no evidence that these deaths were related to gavage trauma, and they were therefore attributed to chemical toxicity. Although 2-year survival was somewhat reduced in the high-dose males, over 50% survived until week 93; similarly, over 50% of low-dose females survived until week 95, and 50% of high-dose females survived to week 103. Survival of high-dose male mice was also lower than that of controls in the 2-year studies; however, 50% of high-dose male mice survived until week 85. As in rats, the increased number of deaths of male mice receiving 100 mg/kg monochloroacetic acid was attributed to chemical toxicity. Although survival of dosed female mice was similar to the controls, mean body weights of the high-dose group were up to 11% lower than the controls after week 70 of the study. The doses administered to rats and mice were therefore considered to be sufficiently challenging, and the survival adequate, for detection of chemical-related neoplasms.

In both rats and mice, there were no increases in neoplasm incidence at any site attributed to the administration of monochloroacetic acid for 2 years. In female rats, uterine endometrial stromal polyps occurred with a dose-related positive trend (2/60, 7/57, 10/60). However, the incidence of these lesions in controls was unusually low, and the incidence in females receiving monochloroacetic acid was actually lower than the mean historical control rate (116/562 or 20.6%, range 10% to 38%). Further, the only malignant endometrial stromal neoplasm occurred in the control group. For these reasons, the marginal increase in uterine stromal polyps in dosed female rats was not considered to be related to the administration of monochloroacetic acid.

In female mice, the incidence of malignant lymphoma (combined lymphocytic, mixed, and undifferentiated variants) decreased with dose (control, 29/60; low-dose, 18/60; high-dose, 13/60), but the reason for this decreased incidence is unknown. Lower body weights are associated with lower incidences of some common spontaneous neoplasms in rodents, but, although high-dose female mice had lower mean body weights than controls, the reduction in body weight in this study was not large, and the mean body weight of the low-dose females was similar to that of controls. Furthermore, lymphoma is not a neoplasm usually associated with body weight changes (Rao *et al.*, 1987).

No nonneoplastic lesions were associated with the administration of monochloroacetic acid to rats for 2 years. Although myocardial lesions occurred in dosed rats in the 13-week studies, the incidences of degenerative and inflammatory lesions of the heart in the 2-year studies were similar among dosed and control rats. The lack of chemical-related myocardial effects is probably related to the lower doses used in the 2-year studies. Also, any subtle effects might have been obscured by the development of spontaneous age-related degenerative changes.

The principal nonneoplastic lesion associated with the administration of monochloroacetic acid to mice for 2 years was focal hyperplasia of the forestomach epithelium. In some mice, the lesions were accompanied by focal erosions, ulcers, or chronic inflammation. Monochloroacetic acid has been shown to be a strong irritant to the skin, eyes, and mucous membranes (Morrison and Leake, 1941; Sax, 1981); thus, the increase in hyperplasia of the forestomach epithelium is likely related to the irritant properties of the chemical. Although squamous cell papillomas occurred in two high-dose females, with none in controls, these two neoplasms could not be attributed to monochloroacetic acid. The incidence of forestomach squamous cell papillomas in historical water gavage controls is 1.3% with as many as three occurring in a single group of mice. Dose-related increases in the incidences of degenerative and inflammatory lesions of the nasal mucosa were observed in male and female mice. These lesions may have resulted from reflux of gavage solution rather than from a systemic effect.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** for monochloroacetic acid in male or female F344/N rats given 15 or 30 mg/kg. There was *no evidence of carcinogenic activity* for monochloroacetic acid in male or female $B6C3F_1$ mice given 50 or 100 mg/kg.

Monochloroacetic acid administration was associated with inflammatory lesions of the nasal mucosa, metaplasia of the olfactory epithelium, and squamous cell hyperplasia of the forestomach in male and female mice.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF MONOCHLOROACETIC ACID

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
Scheduled sacrifice	17	17	17
Early deaths			
Dead	8	11	20
Moribund	17	21	15
Accidental deaths	1	0	2
Survivors			
Terminal sacrifice	27	21	16
Animals examined microscopically	53	53	53
Alimentary System			
Intestine large, cecum	(52)	(52)	(53)
Intestine large, colon	(53)	(53)	(53)
Intestine small, ileum	(53)	(52)	(51)
Carcinoma			1 (2%)
Intestine small, jejunum	(51)	(52)	(52)
Carcinoma		1 (2%)	
Sarcoma			1 (2%)
Liver	(53)	(53)	(53)
Hepatocellular carcinoma		1 (2%)	
Neoplastic nodule	1 (2%)		1 (2%)
Mesentery	(2)	(1)	(2)
Pancreas	(52)	(53)	(52)
Adenoma	1 (2%)	1 (2%)	
Osteosarcoma, metastatic, bone			1 (2%)
Salivary glands	(52)	(53)	(53)
Stomach	(53)	(52)	(53)
Stomach, forestomach	(53)	(52)	(53)
Stomach, glandular	(52)	(52)	(53)
Cardiovascular System			
Heart	(52)	(53)	(53)
Osteosarcoma, metastatic, bone			1 (2%)
Endocrine System			
Adrenal gland, cortex	(52)	(51)	(53)
Osteosarcoma, metastatic, bone			1 (2%)
Adrenal gland, medulla	(51)	(50)	(53)
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma benign	12 (24%)	11 (22%)	8 (15%)
Bilateral, pheochromocytoma benign	5 (10%)	2 (4%)	
Islets, pancreatic	(52)	(53)	(52)
Adenoma	3 (6%)	1 (2%)	1 (2%)
Parathyroid gland	(48)	(47)	(37)
Adenoma		1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Endocrine System (continued)			
Pituitary gland	(53)	(52)	(53)
Pars distalis, adenoma	13 (25%)	6 (12%)	5 (9%)
Thyroid gland	(53)	(53)	(53)
C-cell, adenoma	5 (9%)	2 (4%)	1 (2%)
C-cell, carcinoma	2 (4%)	1 (2%)	
Follicle, adenoma			1 (2%)
General Body System			
Tissue NOS		(1)	
Genital System			
Epididymis	(52)	(50)	(52)
Preputial gland	(51)	(52)	(52)
Papilloma squamous	1 (2%)		
Prostate	(48)	(52)	(53)
Testes	(53)	(51)	(52)
Bilateral, interstitial cell, adenoma	35 (66%)	38 (75%)	39 (75%)
Interstitial cell, adenoma	14 (26%)	9 (18%)	6 (12%)
Hematopoietic System			
Bone marrow	(53)	(52)	(52)
Lymph node	(53)	(52)	(53)
Lymph node, mesenteric	(53)	(52)	(53)
Spleen	(53)	(53)	(53)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Thymus	(47)	(48)	(50)
Integumentary System			
Mammary gland	(53)	(52)	(53)
Adenoma	1 (2%)		
Fibroadenoma	3 (6%)	3 (6%)	3 (6%)
Fibroadenoma, multiple			1 (2%)
Skin	(53)	(51)	(53)
Keratoacanthoma	3 (6%)	3 (6%)	
Squamous cell carcinoma		1 (2%)	1 (2%)
Face, basal cell carcinoma			1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, trichoepithelioma		1 (2%)	
Musculoskeletal System			
Bone	(53)	(52)	(52)
Osteosarcoma			1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Nervous System			
Brain	(53)	(53)	(53)
Astrocytoma malignant	1 (2%)	1 (2%)	
Respiratory System			
Lung	(53)	(53)	(53)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	
Alveolar/bronchiolar carcinoma			1 (2%)
Carcinoma, metastatic, Zymbal's gland	1 (2%)		
Liposarcoma	1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)
Nose	(52)	(53)	(53)
Squamous cell carcinoma	2 (4%)		
Trachea	(53)	(53)	(53)
Special Senses System			
Zymbal's gland	(1)		(1)
Carcinoma	1 (100%)		1 (100%)
Urinary System			
Kidney	(53)	(53)	(53)
Osteosarcoma, metastatic, bone			1 (2%)
Pelvis, transitional epithelium, carcinoma		1 (2%)	
Renal tubule, adenoma	1 (2%)		
Urinary bladder	(51)	(52)	(53)
Papilloma			1 (2%)
Transitional epithelium, papilloma		1 (2%)	
Systemic Lesions			
Multiple organs[a]	(53)	(53)	(53)
Leukemia mononuclear	28 (53%)	30 (57%)	20 (38%)
Mesothelioma benign	1 (2%)	3 (6%)	1 (2%)
Mesothelioma malignant	1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Tumor Summary			
Total animals with primary neoplasms[b]	52	52	46
Total primary neoplasms	138	123	97
Total animals with benign neoplasms	51	50	46
Total benign neoplasms	101	90	71
Total animals with malignant neoplasms	33	33	24
Total malignant neoplasms	37	37	28
Total animals with secondary neoplasms[c]	1		1
Total secondary neoplasms	2		5
Total animals with malignant neoplasms uncertain primary site	1		

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control

Number of Days on Study	2 9 1	3 5 0	4 3 6	4 4 7	5 0 6	5 1 2	5 3 8	5 7 5	5 8 4	5 8 4	5 8 5	6 2 1	6 2 9	6 3 1	6 5 6	6 7 4	6 7 9	6 9 1	6 9 1	6 9 3	7 0 5	7 1 4	7 1 5	7 1 8	7 2 5	7 2 8	7 2 9	7 2 9
Carcass ID Number	0 2 3	0 3 1	1 4 1	0 5 2	1 2 2	0 3 2	0 3 8	1 2 3	0 2 5	1 3 5	0 5 5	0 8 5	0 5 5	1 2 3	1 3 2	0 6 4	0 4 4	1 4 4	0 6 5	1 3 3	0 3 5	0 1 5	0 7 3	0 7 4	0 4 1	1 3 4	1 1 5	0 2 4	0 4 3
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																												
Mesentery								+								+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																				X								
Pheochromocytoma benign								X			X															X	X	X
Bilateral, pheochromocytoma benign																			X				X		X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																					X							X
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X				X	X	X								X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																						
C-cell, carcinoma																												
General Body System																												
None																												
Genital System																												
Epididymis	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																												
Prostate	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Seminal vesicle	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	M

+: 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 Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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 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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 6 3	0 9 3	0 9 4	1 0 2	1 0 3	0 0 5	0 4 4	0 5 2	1 1 4	1 1 4	1 2 4	1 4 3	1 4 5	0 3 3	0 7 5	0 9 1	0 9 5	0 1 4	1 1 3	1 1 3	0 1 4	0 3 4	0 4 2	0 8 4	0 9 2	1 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Neoplastic nodule																					X					1
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																					X					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant																										1
Pheochromocytoma benign		X			X	X		X					X	X	X											12
Bilateral, pheochromocytoma benign											X									X						5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																					X					3
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma					X		X		X	X			X				X								X		13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma		X																X			X		X				5
C-cell, carcinoma			X					X																			2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Preputial gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Papilloma squamous														X												1
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	M	+	+	+	48
Seminal vesicle	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	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	2 9 1	3 5 0	4 3 6	4 4 7	5 0 6	5 1 2	5 3 8	5 7 5	5 8 4	5 8 4	5 8 5	6 2 1	6 2 9	6 3 1	6 5 6	6 7 4	6 7 9	6 9 1	6 9 1	6 9 3	7 0 5	7 1 4	7 1 5	7 1 8	7 2 5	7 2 8	7 2 9	7 2 9
Carcass ID Number	0 2 3	0 3 1	1 4 1	0 5 2	1 2 2	0 3 2	0 3 3	1 2 3	0 2 5	1 3 5	0 5 5	0 8 5	0 2 5	1 3 2	1 6 4	0 4 4	0 4 4	1 4 5	0 6 3	1 3 3	0 1 5	0 7 3	0 7 4	0 4 1	0 3 4	1 1 5	1 2 4	0 4 3
Genital System (continued)																												
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		X	X	X	X	X	X									X						
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																					X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																												
Fibroadenoma																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																												
Subcutaneous tissue, fibroma													X							X								
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+														
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																												
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																					X							
Liposarcoma				X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma		X													X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Ear								+																				
Eye									+	+						+												
Zymbal's gland																					+							
Carcinoma																					X							
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																					X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X		X	X	X	X							X	X	X	X	X		X	X	X		X
Mesothelioma benign																												
Mesothelioma malignant															X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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 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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 6 3	0 9 3	0 9 4	1 0 2	1 0 3	0 4 5	0 5 4	1 1 2	1 1 4	1 2 4	1 4 3	1 4 5	0 4 3	0 7 5	0 9 1	0 9 5	0 1 4	1 1 3	1 1 3	0 1 4	0 3 4	0 4 2	0 8 4	0 9 2	1 0 5	**Total Tissues/ Tumors**
Genital System (continued)																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, interstitial cell, adenoma	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	35
Interstitial cell, adenoma			X			X			X																	14
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic, uncertain primary site																										1
Thymus	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma										X																1
Fibroadenoma							X				X										X					3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Keratoacanthoma										X	X							X								3
Subcutaneous tissue, fibroma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant						X																				1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma, metastatic, Zymbal's gland																										1
Liposarcoma																										1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																										
Ear																										1
Eye		+																								4
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear		X	X	X					X	X	X	X		X	X				X				X		X	28
Mesothelioma benign											X															1
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	7 1 8	7 2 5	7 2 8	7 2 8	7 2 9	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	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 2 2	3 5 5	3 5 4	3 9 4	2 9 4	3 6 2	3 7 4	3 7 5	3 1 5	3 2 2	3 2 5	3 4 4	3 6 4	3 8 3	3 0 5	3 4 5	3 8 4	3 8 5	3 9 3	4 0 4	2 9 5	3 1 4	3 3 2	3 3 4	4 0 3	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hepatocellular carcinoma																									1
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																									1
Pheochromocytoma benign		X	X		X				X									X	X				X	X	11
Bilateral, pheochromocytoma benign								X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																			X						1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	47
Adenoma																			X						1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma											X								X			X		X	6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma														X							X				2
C-cell, carcinoma															X										1
General Body System																									
Tissue NOS																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Seminal vesicle	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	2 8 4	3 6 4	4 1 1	4 2 7	4 4 8	5 5 6	5 5 7	5 5 7	5 6 9	5 8 8	5 9 9	6 0 2	6 1 1	6 2 5	6 3 3	6 3 3	6 4 4	6 4 7	6 4 7	6 4 7	6 6 8	6 8 6	6 8 7	6 9 6	7 0 6	7 0 6	7 1 8	7 1 8
Carcass ID Number	3 9 2	2 9 1	4 1 1	4 1 2	3 1 1	3 4 2	2 9 3	4 0 2	3 0 3	3 5 3	4 2 4	4 0 5	3 6 3	3 3 3	3 2 3	4 1 5	3 0 4	4 1 3	4 1 4	4 2 3	4 2 5	3 2 4	3 6 5	3 9 5	3 1 3	3 3 1	3 2 5	3 4 3
Genital System (continued)																												
Testes	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Bilateral, interstitial cell, adenoma					X		X		X	X	X			X			X	X	X	X	X	X	X			X	X	X
Interstitial cell, adenoma				X								X	X		X	X								X				
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	I	I	
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																X												
Skin	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X		X											
Squamous cell carcinoma																												
Subcutaneous tissue, fibroma																												X
Subcutaneous tissue, trichoepithelioma																												
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant		X																										
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple																	X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Eye														+					+									
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, carcinoma																												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Transitional epithelium, papilloma																												
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X					X	X	X	X				X	X	X	X	X	X	X	X		X
Mesothelioma benign																			X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	7 1 8	7 2 5	7 2 8	7 2 8	7 2 9	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	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 2 2	3 5 5	3 5 4	3 9 4	2 9 4	3 6 2	3 7 4	3 7 5	3 1 5	3 2 2	3 2 5	3 4 4	3 6 4	3 8 3	3 0 5	3 4 5	3 8 4	3 8 5	3 9 3	4 0 4	2 9 5	3 1 4	3 3 2	3 3 4	4 0 3	**Total Tissues/ Tumors**
Genital System (continued)																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	38
Interstitial cell, adenoma			X															X			X					9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibroadenoma												X		X												3
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Keratoacanthoma		X																								3
Squamous cell carcinoma		X																								1
Subcutaneous tissue, fibroma																X						X				3
Subcutaneous tissue, trichoepithelioma																				X						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar adenoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																										
Eye																		+								3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pelvis, transitional epithelium, carcinoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional epithelium, papilloma																			X							1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X	X		X	X	X	X	X		X			X	X			X	X		X				X	X	30
Mesothelioma benign																				X		X				3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg

Number of Days on Study	3 3 3 3 3 3 4 4 4 4 4 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 3 3 4 5 5 6 1 5 5 7 8 9 1 1 2 2 3 3 5 6 6 7 2 3 3 3 4 5 6 9 4 1 9 6 7 0 7 7 6 2 3 9 2 8 2 5 6 4 4 7 4 2 2 8 2 3
Carcass ID Number	7 6 6 6 7 6 6 6 6 5 5 6 7 6 5 6 7 6 6 5 6 6 5 5 6 6 5 6 0 3 7 1 0 5 6 9 5 8 9 7 0 4 8 2 0 9 1 7 8 3 7 8 1 2 9 3 1 1 5 2 2 2 2 2 3 2 4 1 3 1 3 2 4 3 1 3 2 4 4 4 5 5 5 3
Alimentary System	
Esophagus	+ +
Intestine large	+ +
Intestine large, cecum	+ +
Intestine large, colon	+ +
Intestine large, rectum	+ + + + + I +
Intestine small	+ +
Intestine small, duodenum	+ +
Intestine small, ileum	+ + + + + + A + + + + + + + + + + + + + + + + + + +
Carcinoma	X
Intestine small, jejunum	+ + + + + + A + + + + + + + + + + + + + + + + + + +
Sarcoma	
Liver	+ +
Neoplastic nodule	
Mesentery	+
Pancreas	+ + + + + + + I + + + + + + + + + + + + + + + + + +
Osteosarcoma, metastatic, bone	X
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tongue	+
Cardiovascular System	
Blood vessel	+ M +
Heart	+ +
Osteosarcoma, metastatic, bone	X
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Osteosarcoma, metastatic, bone	X
Adrenal gland, medulla	+ +
Pheochromocytoma malignant	
Pheochromocytoma benign	X
Islets, pancreatic	+ + + + + + + I + + + + + + + + + + + + + + + + + +
Adenoma	
Parathyroid gland	+ + + + M + M + + + + + M + + + + M M + + M M + M + + +
Pituitary gland	+ +
Pars distalis, adenoma	X
Thyroid gland	+ +
C-cell, adenoma	X
Follicle, adenoma	
General Body System	
None	
Genital System	
Epididymis	+ M + + + + + +
Penis	+
Preputial gland	+ + + + + + + + M + + + + + + + + + + + + + + + + + +
Prostate	+ +
Seminal vesicle	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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	6 5 7	6 6 6	6 6 9	6 7 2	6 8 2	6 9 0	6 9 8	7 1 8	7 1 8	7 2 9	7 2 9	7 2 9	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 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	6 0 4	6 7 4	6 4 3	6 6 4	6 4 4	6 0 5	6 2 3	6 1 4	6 5 5	6 1 3	6 2 4	6 7 3	7 0 5	6 3 5	6 4 5	6 8 3	6 9 5	6 4 2	6 6 5	6 8 5	6 9 4	5 8 5	6 5 4	6 7 2	6 8 4	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma																									1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma																					X				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Neoplastic nodule																X									1
Mesentery																					+				2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Osteosarcoma, metastatic, bone																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																						+			3
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic, bone																									1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic, bone																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pheochromocytoma malignant						X																			1
Pheochromocytoma benign										X		X		X			X	X	X			X			8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma							X																		1
Parathyroid gland	+	M	+	M	+	+	+	I	+	M	+	M	+	+	M	+	+	+	+	+	+	M	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma			X				X								X							X			5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
C-cell, adenoma																									1
Follicle, adenoma								X																	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Penis																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Seminal vesicle	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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	3 3 3 3 3 3 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 3 3 4 5 5 6 1 5 5 7 8 9 1 1 2 2 3 3 5 6 6 7 2 3 3 3 4 5 6 9 4 1 9 6 7 0 7 7 6 2 3 9 2 8 2 5 6 4 4 7 4 2 2 8 2 3
Carcass ID Number	7 6 6 6 7 6 6 6 6 5 5 6 7 6 5 6 7 6 6 5 6 6 5 5 6 6 5 6 0 3 7 1 0 5 6 9 5 8 9 7 0 4 8 2 0 9 1 7 8 3 7 8 1 2 9 3 1 1 5 2 2 2 2 2 3 2 4 1 3 1 3 2 4 3 1 3 2 4 4 4 5 5 5 3
Genital System (continued)	
Testes	+ M + + + + + +
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X X X X X X X X X X
Interstitial cell, adenoma	X X X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	+ + + + I + + + + + + + + + + + + + + + I + + + + + + +
Integumentary System	
Mammary gland	+ +
Fibroadenoma	
Fibroadenoma, multiple	
Skin	+ +
Squamous cell carcinoma	X
Face, basal cell carcinoma	
Subcutaneous tissue, fibroma	X
Musculoskeletal System	
Bone	+ +
Osteosarcoma	X
Skeletal muscle	+
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar carcinoma	
Osteosarcoma, metastatic, bone	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+
Zymbal's gland	+
Carcinoma	X
Urinary System	
Kidney	+ +
Osteosarcoma, metastatic, bone	X
Urinary bladder	+ +
Papilloma	
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X
Mesothelioma benign	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	6 5 7	6 6 6	6 6 9	6 7 2	6 8 2	6 9 0	6 9 8	7 1 8	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	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 2	7 3 2	7 3 2	
Carcass ID Number	6 0 4	6 7 4	6 4 3	6 6 4	6 4 4	6 0 5	6 2 3	6 1 4	6 5 5	6 1 3	6 2 4	6 7 3	7 0 5	6 3 5	6 4 5	6 8 3	6 9 5	6 4 2	6 6 5	6 8 5	6 9 4	5 8 5	6 5 4	6 7 2	6 8 4	**Total Tissues/ Tumors**
Genital System (continued)																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	39
Interstitial cell, adenoma														X											6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Fibroadenoma					X										X							X			3
Fibroadenoma, multiple																							X		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Squamous cell carcinoma																									1
Face, basal cell carcinoma																X									1
Subcutaneous tissue, fibroma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		52
Osteosarcoma																									1
Skeletal muscle																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Alveolar/bronchiolar carcinoma																					X				1
Osteosarcoma, metastatic, bone																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																									
Eye																	+	+							3
Zymbal's gland																									1
Carcinoma																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Osteosarcoma, metastatic, bone																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Papilloma																				X					1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X		X	X	X	X		X		X	X			X		X				X			X		20
Mesothelioma benign																									1

TABLE A3
Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Adrenal Medulla: Pheochromocytoma (Benign)			
Overall rates[a]	17/51 (33%)	13/50 (26%)	8/53 (15%)
Adjusted rates[b]	50.4%	46.3%	45.5%
Terminal rates[c]	11/27 (41%)	7/21 (33%)	7/16 (44%)
First incidence (days)	575	644	577
Life table tests[d]	P=0.308N	P=0.499N	P=0.333N
Logistic regression tests[d]	P=0.159N	P=0.322N	P=0.188N
Cochran-Armitage test[d]	P=0.020N		
Fisher exact test[d]		P=0.278N	P=0.025N
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)			
Overall rates	18/51 (35%)	14/50 (28%)	9/53 (17%)
Adjusted rates	51.9%	48.0%	48.2%
Terminal rates	11/27 (41%)	7/21 (33%)	7/16 (44%)
First incidence (days)	575	644	577
Life table tests	P=0.362N	P=0.509N	P=0.391N
Logistic regression tests	P=0.176N	P=0.325N	P=0.209N
Cochran-Armitage test	P=0.023N		
Fisher exact test		P=0.283N	P=0.028N
Mammary Gland: Fibroadenoma			
Overall rates	3/53 (6%)	3/53 (6%)	4/53 (8%)
Adjusted rates	11.1%	11.8%	22.6%
Terminal rates	3/27 (11%)	2/21 (10%)	3/16 (19%)
First incidence (days)	729 (T)	633	682
Life table tests	P=0.186	P=0.564	P=0.229
Logistic regression tests	P=0.210	P=0.624	P=0.231
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.661N	P=0.500
Mammary Gland: Adenoma or Fibroadenoma			
Overall rates	4/53 (8%)	3/53 (6%)	4/53 (8%)
Adjusted rates	14.8%	11.8%	22.6%
Terminal rates	4/27 (15%)	2/21 (10%)	3/16 (19%)
First incidence (days)	729 (T)	633	682
Life table tests	P=0.299	P=0.618N	P=0.340
Logistic regression tests	P=0.330	P=0.553N	P=0.340
Cochran-Armitage test	P=0.576N		
Fisher exact test		P=0.500N	P=0.642N
Pancreatic Islets: Adenoma			
Overall rates	3/52 (6%)	1/53 (2%)	1/52 (2%)
Adjusted rates	10.2%	4.8%	5.3%
Terminal rates	2/27 (7%)	1/21 (5%)	0/16 (0%)
First incidence (days)	705	729 (T)	698
Life table tests	P=0.361N	P=0.387N	P=0.516N
Logistic regression tests	P=0.321N	P=0.342N	P=0.464N
Cochran-Armitage test	P=0.201N		
Fisher exact test		P=0.302N	P=0.309N

TABLE A3
Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	13/53 (25%)	6/52 (12%)	5/53 (9%)
Adjusted rates	39.0%	22.4%	22.6%
Terminal rates	8/27 (30%)	4/21 (19%)	2/16 (13%)
First incidence (days)	621	556	513
Life table tests	P=0.156N	P=0.149N	P=0.253N
Logistic regression tests	P=0.061N	P=0.080N	P=0.127N
Cochran-Armitage test	P=0.021N		
Fisher exact test		P=0.069N	P=0.034N
Skin: Keratoacanthoma			
Overall rates	3/53 (6%)	3/53 (6%)	0/53 (0%)
Adjusted rates	11.1%	9.1%	0.0%
Terminal rates	3/27 (11%)	0/21 (0%)	0/16 (0%)
First incidence (days)	729 (T)	633	-[e]
Life table tests	P=0.209N	P=0.583	P=0.225N
Logistic regression tests	P=0.158N	P=0.642	P=0.225N
Cochran-Armitage test	P=0.101N		
Fisher exact test		P=0.661N	P=0.121N
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	2/53 (4%)	3/53 (6%)	1/53 (2%)
Adjusted rates	5.3%	12.9%	2.6%
Terminal rates	0/27 (0%)	2/21 (10%)	0/16 (0%)
First incidence (days)	629	718	522
Life table tests	P=0.570N	P=0.430	P=0.623N
Logistic regression tests	P=0.454N	P=0.477	P=0.469N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.500	P=0.500N
Testes: Adenoma			
Overall rates	49/53 (92%)	47/51 (92%)	45/52 (87%)
Adjusted rates	98.0%	100.0%	100.0%
Terminal rates	26/27 (96%)	21/21 (100%)	16/16 (100%)
First incidence (days)	436	427	450
Life table tests	P=0.013	P=0.248	P=0.018
Logistic regression tests	P=0.306	P=0.590N	P=0.445
Cochran-Armitage test	P=0.195N		
Fisher exact test		P=0.620N	P=0.252N
Thyroid Gland (C-Cell): Adenoma			
Overall rates	5/53 (9%)	2/53 (4%)	1/53 (2%)
Adjusted rates	16.6%	9.5%	3.8%
Terminal rates	4/27 (15%)	2/21 (10%)	0/16 (0%)
First incidence (days)	512	729 (T)	653
Life table tests	P=0.150N	P=0.309N	P=0.233N
Logistic regression tests	P=0.099N	P=0.235N	P=0.153N
Cochran-Armitage test	P=0.060N		
Fisher exact test		P=0.219N	P=0.103N

TABLE A3
Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rates	7/53 (13%)	3/53 (6%)	1/53 (2%)
Adjusted rates	23.8%	14.3%	3.8%
Terminal rates	6/27 (22%)	3/21 (14%)	0/16 (0%)
First incidence (days)	512	729 (T)	653
Life table tests	P=0.067N	P=0.258N	P=0.112N
Logistic regression tests	P=0.043N	P=0.185N	P=0.070N
Cochran-Armitage test	P=0.018N		
Fisher exact test		P=0.160N	P=0.030N
All Organs: Mononuclear Leukemia			
Overall rates	28/53 (53%)	30/53 (57%)	20/53 (38%)
Adjusted rates	65.5%	75.6%	63.7%
Terminal rates	13/27 (48%)	12/21 (57%)	6/16 (38%)
First incidence (days)	436	448	492
Life table tests	P=0.311	P=0.202	P=0.391
Logistic regression tests	P=0.246N	P=0.383	P=0.244N
Cochran-Armitage test	P=0.073N		
Fisher exact test		P=0.423	P=0.086N
All Organs: Mesothelioma Benign and Malignant			
Overall rates	2/53 (4%)	3/53 (6%)	1/53 (2%)
Adjusted rates	6.2%	12.0%	2.2%
Terminal rates	1/27 (4%)	2/21 (10%)	0/16 (0%)
First incidence (days)	656	647	450
Life table tests	P=0.563N	P=0.410	P=0.617N
Logistic regression tests	P=0.425N	P=0.479	P=0.464N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.500	P=0.500N
All Organs: Benign Tumors			
Overall rates	51/53 (96%)	50/53 (94%)	46/53 (87%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	27/27 (100%)	21/21 (100%)	16/16 (100%)
First incidence (days)	436	427	450
Life table tests	P=0.016	P=0.204	P=0.021
Logistic regression tests	P=0.398N	P=0.398N	P=0.464N
Cochran-Armitage test	P=0.049N		
Fisher exact test		P=0.500N	P=0.080N
All Organs: Malignant Tumors			
Overall rates	33/53 (62%)	33/53 (62%)	24/53 (45%)
Adjusted rates	72.3%	79.2%	69.8%
Terminal rates	15/27 (56%)	13/21 (62%)	7/16 (44%)
First incidence (days)	350	364	486
Life table tests	P=0.317	P=0.283	P=0.381
Logistic regression tests	P=0.107N	P=0.573	P=0.125N
Cochran-Armitage test	P=0.048N		
Fisher exact test		P=0.579N	P=0.059N

TABLE A3
Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	15 mg/kg	30 mg/kg
All Organs: Benign and Malignant Tumors			
Overall rates	52/53 (98%)	52/53 (98%)	46/53 (87%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	27/27 (100%)	21/21 (100%)	16/16 (100%)
First incidence (days)	350	364	450
Life table tests	P=0.024	P=0.174	P=0.030
Logistic regression tests	P=0.010N	P=0.807	P=0.092N
Cochran-Armitage test	P=0.010N		
Fisher exact test		P=0.752N	P=0.030N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
Scheduled sacrifice	17	17	17
Early deaths			
Dead	8	11	20
Moribund	17	21	15
Accidental deaths	1	0	2
Survivors			
Terminal sacrifice	27	21	16
Animals examined microscopically	53	53	53
Alimentary System			
Esophagus	(53)	(53)	(53)
Wall, inflammation, chronic			1 (2%)
Intestine large, cecum	(52)	(52)	(53)
Autolysis		1 (2%)	
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)
Parasite metazoan	1 (2%)		
Intestine large, colon	(53)	(53)	(53)
Hyperplasia, lymphoid		1 (2%)	
Infiltration cellular, lymphocytic	1 (2%)		
Parasite metazoan	11 (21%)	6 (11%)	12 (23%)
Intestine large, rectum	(53)	(52)	(52)
Inflammation, acute	1 (2%)		
Parasite metazoan	5 (9%)		2 (4%)
Intestine small	(53)	(53)	(53)
Perivascular, inflammation, chronic			1 (2%)
Serosa, inflammation, chronic			1 (2%)
Intestine small, duodenum	(52)	(53)	(53)
Autolysis	1 (2%)		
Inflammation, chronic			1 (2%)
Necrosis, acute, focal			1 (2%)
Intestine small, ileum	(53)	(52)	(51)
Autolysis	1 (2%)	3 (6%)	1 (2%)
Parasite metazoan			1 (2%)
Intestine small, jejunum	(51)	(52)	(52)
Autolysis	1 (2%)	2 (4%)	
Liver	(53)	(53)	(53)
Angiectasis	1 (2%)		
Angiectasis, focal	1 (2%)	1 (2%)	
Basophilic focus	9 (17%)	1 (2%)	5 (9%)
Basophilic focus, multiple	3 (6%)	10 (19%)	3 (6%)
Clear cell focus		1 (2%)	1 (2%)
Congestion	1 (2%)	2 (4%)	1 (2%)
Cytoplasmic alteration, focal	9 (17%)	3 (6%)	4 (8%)
Cytoplasmic alteration, multifocal	2 (4%)		
Fatty change, diffuse	1 (2%)		
Fatty change, multifocal	1 (2%)		
Hepatodiaphragmatic nodule		2 (4%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Alimentary System (continued)			
Liver (continued)			
Hyperplasia, focal		1 (2%)	
Inflammation, acute, multifocal			1 (2%)
Inflammation, chronic		3 (6%)	
Inflammation, granulomatous, multifocal	1 (2%)	3 (6%)	
Necrosis, acute, focal	2 (4%)	1 (2%)	3 (6%)
Pigmentation, diffuse	1 (2%)		
Thrombus	1 (2%)	1 (2%)	
Vacuolization cytoplasmic, focal	1 (2%)	1 (2%)	2 (4%)
Artery, thrombus	1 (2%)		
Bile duct, hyperplasia	20 (38%)	11 (21%)	17 (32%)
Centrilobular, fatty change		1 (2%)	1 (2%)
Centrilobular, vacuolization cytoplasmic		1 (2%)	
Hepatocyte, degeneration, cystic, focal	5 (9%)	3 (6%)	2 (4%)
Hepatocyte, hypertrophy, focal			1 (2%)
Mesentery	(2)	(1)	(2)
Inflammation, chronic			1 (50%)
Fat, necrosis, chronic, multifocal	1 (50%)		
Fat, necrosis, focal		1 (100%)	
Pancreas	(52)	(53)	(52)
Atrophy, focal	16 (31%)	20 (38%)	14 (27%)
Congestion, focal		1 (2%)	
Cytoplasmic alteration, focal	1 (2%)		
Hyperplasia, focal		1 (2%)	
Infiltration cellular, lymphocytic, focal			1 (2%)
Inflammation, chronic		1 (2%)	
Artery, inflammation, chronic	1 (2%)		
Artery, mineralization		1 (2%)	
Duct, ectasia, focal		1 (2%)	1 (2%)
Perivascular, inflammation, chronic			2 (4%)
Salivary glands	(52)	(53)	(53)
Atrophy, diffuse	1 (2%)		
Inflammation, acute, focal		3 (6%)	
Inflammation, chronic		1 (2%)	2 (4%)
Duct, ectasia, focal	1 (2%)		
Duct, inflammation, acute		1 (2%)	
Duct, inflammation, chronic active			1 (2%)
Periductular, inflammation, chronic			1 (2%)
Stomach	(53)	(52)	(53)
Perivascular, inflammation, chronic			1 (2%)
Serosa, inflammation, chronic			1 (2%)
Stomach, forestomach	(53)	(52)	(53)
Hyperplasia	1 (2%)		
Inflammation, acute	3 (6%)	4 (8%)	3 (6%)
Inflammation, chronic	2 (4%)		1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)
Mineralization		1 (2%)	2 (4%)
Necrosis, focal	1 (2%)		
Epithelium, hyperplasia	2 (4%)	6 (12%)	2 (4%)
Serosa, inflammation, chronic			1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Alimentary System (continued)			
Stomach, glandular	(52)	(52)	(53)
Hemorrhage, focal			1 (2%)
Infiltration cellular, lymphocytic		4 (8%)	
Infiltration cellular, lymphocytic, focal			4 (8%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active		1 (2%)	
Mineralization	1 (2%)	4 (8%)	3 (6%)
Necrosis, focal	2 (4%)	5 (10%)	2 (4%)
Tongue			(3)
Epithelium, hyperplasia, focal			2 (67%)
Cardiovascular System			
Blood vessel	(53)	(53)	(52)
Inflammation, acute		1 (2%)	
Aorta, mineralization		1 (2%)	2 (4%)
Heart	(52)	(53)	(53)
Fibrosis, focal	2 (4%)		
Inflammation, chronic	48 (92%)	45 (85%)	46 (87%)
Mineralization	2 (4%)	3 (6%)	2 (4%)
Artery, mineralization, multifocal	1 (2%)		
Atrium left, thrombus	5 (10%)	4 (8%)	3 (6%)
Perivascular, inflammation, chronic			1 (2%)
Valve, thrombus	2 (4%)	1 (2%)	
Endocrine System			
Adrenal gland, cortex	(52)	(51)	(53)
Cyst		1 (2%)	
Hemorrhage, focal			1 (2%)
Hyperplasia		1 (2%)	
Hyperplasia, focal	9 (17%)	8 (16%)	12 (23%)
Hypertrophy, focal	5 (10%)	5 (10%)	3 (6%)
Necrosis, focal	1 (2%)	2 (4%)	
Vacuolization cytoplasmic, diffuse	2 (4%)		
Vacuolization cytoplasmic, focal	7 (13%)	10 (20%)	5 (9%)
Adrenal gland, medulla	(51)	(50)	(53)
Hyperplasia, focal	10 (20%)	6 (12%)	7 (13%)
Mineralization, focal			1 (2%)
Thrombus		1 (2%)	1 (2%)
Bilateral, hyperplasia, focal		1 (2%)	
Islets, pancreatic	(52)	(53)	(52)
Hyperplasia, focal	1 (2%)		
Parathyroid gland	(48)	(47)	(37)
Hyperplasia		3 (6%)	4 (11%)
Hyperplasia, focal		1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Endocrine System (continued)			
Pituitary gland	(53)	(52)	(53)
Hemorrhage		1 (2%)	
Pars distalis, angiectasis	1 (2%)	3 (6%)	1 (2%)
Pars distalis, cyst	2 (4%)	2 (4%)	1 (2%)
Pars distalis, hyperplasia	8 (15%)	7 (13%)	6 (11%)
Pars intermedia, hyperplasia, focal		1 (2%)	
Pars nervosa, hyperplasia	1 (2%)		
Thyroid gland	(53)	(53)	(53)
Ultimobranchial cyst	1 (2%)		
C-cell, hyperplasia	11 (21%)	6 (11%)	4 (8%)
Follicular cell, hyperplasia	3 (6%)		
General Body System			
None			
Genital System			
Epididymis	(52)	(50)	(52)
Duct, epithelium, degeneration	1 (2%)		
Penis			(1)
Inflammation, acute			1 (100%)
Preputial gland	(51)	(52)	(52)
Cyst		1 (2%)	
Ectasia			1 (2%)
Hyperplasia		2 (4%)	
Inflammation, acute	10 (20%)	7 (13%)	8 (15%)
Inflammation, chronic	18 (35%)	28 (54%)	16 (31%)
Inflammation, chronic active		1 (2%)	
Duct, hyperplasia, squamous	1 (2%)		
Prostate	(48)	(52)	(53)
Hyperplasia, focal	4 (8%)	4 (8%)	1 (2%)
Inflammation, acute	6 (13%)		4 (8%)
Inflammation, chronic	1 (2%)	5 (10%)	2 (4%)
Inflammation, chronic active		2 (4%)	
Mineralization			2 (4%)
Epithelium, degeneration, focal	1 (2%)		
Testes	(53)	(51)	(52)
Atrophy	6 (11%)	6 (12%)	1 (2%)
Hemorrhage			1 (2%)
Infarct, diffuse			1 (2%)
Mineralization, focal	1 (2%)		
Bilateral, interstitial cell, hyperplasia	1 (2%)	1 (2%)	
Interstitial cell, hyperplasia	6 (11%)	6 (12%)	6 (12%)
Seminiferous tubule, degeneration	1 (2%)		1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Hematopoietic System			
Bone marrow	(53)	(52)	(52)
Hyperplasia	2 (4%)	2 (4%)	
Hyperplasia, megakaryocyte	1 (2%)		
Hypoplasia	2 (4%)		2 (4%)
Myelofibrosis		2 (4%)	2 (4%)
Myeloid cell, hyperplasia	2 (4%)	3 (6%)	1 (2%)
Lymph node	(53)	(52)	(53)
Axillary, congestion	1 (2%)		
Axillary, hyperplasia		1 (2%)	
Iliac, hyperplasia, plasma cell	1 (2%)		
Iliac, inflammation, granulomatous, focal	1 (2%)		
Inguinal, infiltration cellular, plasma cell		1 (2%)	
Inguinal, inflammation, acute, multifocal	1 (2%)		
Mediastinal, congestion	5 (9%)		2 (4%)
Mediastinal, hemorrhage		1 (2%)	
Mediastinal, hyperplasia	1 (2%)	1 (2%)	
Pancreatic, congestion	1 (2%)		
Pancreatic, fibrosis, focal			1 (2%)
Pancreatic, inflammation, chronic		1 (2%)	
Renal, hemorrhage		1 (2%)	
Lymph node, mesenteric	(53)	(52)	(53)
Congestion	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		2 (4%)	
Hyperplasia	1 (2%)	1 (2%)	
Hyperplasia, re cell			1 (2%)
Necrosis, focal		1 (2%)	
Spleen	(53)	(53)	(53)
Congestion			2 (4%)
Fibrosis	1 (2%)	5 (9%)	1 (2%)
Fibrosis, focal	1 (2%)		
Hematopoietic cell proliferation		2 (4%)	
Hematopoietic cell proliferation granulocytic	2 (4%)	1 (2%)	1 (2%)
Hemorrhage, multifocal	1 (2%)		
Necrosis, focal		1 (2%)	
Pigmentation, diffuse	1 (2%)		
Capsule, fibrosis, focal	2 (4%)		
Thymus	(47)	(48)	(50)
Congestion			2 (4%)
Cyst, multiple	1 (2%)		3 (6%)
Ectasia		1 (2%)	
Hemorrhage	2 (4%)		
Hyperplasia		1 (2%)	2 (4%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Integumentary System			
Mammary gland	(53)	(52)	(53)
Fibrosis		1 (2%)	
Hyperplasia	2 (4%)	6 (12%)	9 (17%)
Hyperplasia, cystic	1 (2%)		2 (4%)
Mineralization		1 (2%)	
Pigmentation		1 (2%)	1 (2%)
Duct, ectasia	2 (4%)	8 (15%)	
Skin	(53)	(51)	(53)
Hemorrhage		1 (2%)	
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic, focal			1 (2%)
Inflammation, chronic active		1 (2%)	
Face, inflammation, acute, focal			1 (2%)
Subcutaneous tissue, edema		1 (2%)	
Subcutaneous tissue, inflammation, acute	1 (2%)		
Subcutaneous tissue, necrosis	1 (2%)		
Musculoskeletal System			
Bone	(53)	(52)	(52)
Fibrous osteodystrophy	1 (2%)	4 (8%)	3 (6%)
Nervous System			
Brain	(53)	(53)	(53)
Congestion	1 (2%)		
Hemorrhage, focal	1 (2%)	1 (2%)	1 (2%)
Hydrocephalus			1 (2%)
Cerebellum, pigmentation, focal			1 (2%)
Meninges, vein, cerebrum, thrombus		1 (2%)	
Thalamus, inflammation, chronic, focal			1 (2%)
Respiratory System			
Lung	(53)	(53)	(53)
Congestion	2 (4%)	6 (11%)	10 (19%)
Fibrosis, multifocal		2 (4%)	
Hemorrhage, focal		2 (4%)	
Inflammation, acute, focal	2 (4%)		
Inflammation, chronic	3 (6%)	4 (8%)	4 (8%)
Inflammation, granulomatous, focal	4 (8%)		
Mineralization, focal	1 (2%)		
Alveolar epithelium, hyperplasia		1 (2%)	
Alveolar epithelium, hyperplasia, focal		1 (2%)	
Alveolus, infiltration cellular, histiocytic	2 (4%)	4 (8%)	1 (2%)
Alveolus, pigmentation		1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Respiratory System (continued)			
Lung (continued)			
Artery, media, hypertrophy		1 (2%)	
Bronchiole, inflammation, chronic active, multifocal			1 (2%)
Peribronchial, infiltration cellular, lymphocytic			1 (2%)
Perivascular, inflammation, chronic	4 (8%)	2 (4%)	2 (4%)
Pleura, fibrosis, focal			1 (2%)
Pleura, infiltration cellular, histiocytic, focal			1 (2%)
Subpleura, inflammation, chronic			2 (4%)
Nose	(52)	(53)	(53)
Autolysis		2 (4%)	3 (6%)
Congestion			2 (4%)
Cyst	3 (6%)		
Foreign body		3 (6%)	
Fungus	8 (15%)	8 (15%)	5 (9%)
Metaplasia, squamous			6 (11%)
Mucosa, concretion, focal	1 (2%)		
Mucosa, inflammation, acute	7 (13%)	4 (8%)	9 (17%)
Mucosa, inflammation, chronic		3 (6%)	
Mucosa, inflammation, chronic active	9 (17%)	8 (15%)	15 (28%)
Nasolacrimal duct, inflammation, acute	3 (6%)	1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, chronic	1 (2%)		2 (4%)
Respiratory epithelium, hyperplasia	2 (4%)		
Respiratory epithelium, hyperplasia, papillary		1 (2%)	
Vomeronasal organ, inflammation, acute			1
Trachea	(53)	(53)	(53)
Inflammation, chronic	2 (4%)		2 (4%)
Special Senses System			
Eye	(4)	(3)	(3)
Bilateral, lens, cataract		1 (33%)	1 (33%)
Lens, cataract	2 (50%)	1 (33%)	2 (67%)
Retina, degeneration	1 (25%)		2 (67%)
Sclera, mineralization, focal	3 (75%)	3 (100%)	1 (33%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Urinary System			
Kidney	(53)	(53)	(53)
Autolysis		6 (11%)	
Calculus micro observation only	1 (2%)		
Congestion		1 (2%)	1 (2%)
Mineralization, multifocal	1 (2%)		
Nephropathy	53 (100%)	51 (96%)	48 (91%)
Cortex, cyst	1 (2%)	2 (4%)	
Medulla, inflammation, multifocal	1 (2%)		
Pelvis, calculus gross observation	1 (2%)		
Pelvis, inflammation, acute	2 (4%)	1 (2%)	
Pelvis, transitional epithelium, hyperplasia	2 (4%)	3 (6%)	2
Renal tubule, epithelium, pigmentation	3 (6%)	1 (2%)	1 (2%)
Urinary bladder	(51)	(52)	(53)
Hemorrhage		1 (2%)	
Inflammation, acute	2 (4%)		1 (2%)
Transitional epithelium, hyperplasia		1 (2%)	
Transitional epithelium, hyperplasia, papillary, focal			1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF MONOCHLOROACETIC ACID

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
Scheduled sacrifice	17	17	17
Early deaths			
Moribund	14	21	13
Dead	2	11	13
Accidental deaths	0	2	1
Survivors			
Terminal sacrifice	37	19	25
Moribund	0	0	1
Animals examined microscopically	53	53	53
Alimentary System			
Intestine large, colon	(53)	(53)	(51)
Intestine small, ileum	(53)	(53)	(48)
Liver	(53)	(53)	(53)
Neoplastic nodule	1 (2%)		
Mesentery	(4)		(2)
Pancreas	(53)	(53)	(51)
Salivary glands	(53)	(53)	(53)
Stomach, forestomach	(51)	(52)	(53)
Stomach, glandular	(53)	(53)	(53)
Tongue	(1)		(3)
Papilloma squamous	1 (100%)		1 (33%)
Cardiovascular System			
Heart	(53)	(53)	(53)
Endocrine System			
Adrenal gland, cortex	(53)	(53)	(52)
Adenoma			1 (2%)
Adrenal gland, medulla	(52)	(52)	(53)
Pheochromocytoma benign	2 (4%)		
Islets, pancreatic	(53)	(53)	(51)
Carcinoma			1 (2%)
Pituitary gland	(53)	(53)	(53)
Pars distalis, adenoma	26 (49%)	19 (36%)	17 (32%)
Pars distalis, carcinoma	2 (4%)	2 (4%)	
Thyroid gland	(53)	(52)	(52)
Bilateral, C-cell, adenoma	1 (2%)		
C-cell, adenoma	5 (9%)	3 (6%)	3 (6%)
C-cell, carcinoma	2 (4%)		2 (4%)
General Body System			
None			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Genital System			
Clitoral gland	(44)	(45)	(48)
Carcinoma		1 (2%)	
Sarcoma			1 (2%)
Ovary	(53)	(53)	(53)
Adenoma	1 (2%)		
Granulosa cell tumor malignant		1 (2%)	
Granulosa cell tumor benign	1 (2%)		
Uterus	(53)	(53)	(53)
Sarcoma stromal	1 (2%)		
Endometrium, polyp stromal	1 (2%)	7 (13%)	9 (17%)
Hematopoietic System			
Bone marrow	(53)	(53)	(53)
Lymph node	(53)	(52)	(53)
Mediastinal, sarcoma	1 (2%)		
Lymph node, mesenteric	(52)	(52)	(53)
Spleen	(53)	(53)	(53)
Thymus	(51)	(51)	(44)
Sarcoma	1 (2%)		
Integumentary System			
Mammary gland	(53)	(53)	(51)
Carcinoma	2 (4%)	3 (6%)	2 (4%)
Fibroadenoma	26 (49%)	23 (43%)	21 (41%)
Fibroadenoma, multiple	1 (2%)		1 (2%)
Skin	(53)	(52)	(52)
Carcinoma		1 (2%)	
Keratoacanthoma			1 (2%)
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	
Musculoskeletal System			
None			
Nervous System			
Brain	(53)	(53)	(53)
Astrocytoma malignant	2 (4%)	1 (2%)	
Carcinoma, early invasion, metastatic, pituitary gland	1 (2%)	1 (2%)	
Spinal cord	(1)		
Respiratory System			
Lung	(53)	(53)	(53)
Nose	(52)	(53)	(48)
Trachea	(53)	(53)	(53)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Special Senses System			
Zymbal's gland	(1)	(1)	
Carcinoma	1 (100%)	1 (100%)	
Urinary System			
Kidney	(53)	(53)	(52)
Hemangiosarcoma		1 (2%)	
Urinary bladder	(52)	(52)	(49)
Transitional epithelium, carcinoma	1 (2%)		
Systemic Lesions			
Multiple organs[a]	(53)	(53)	(53)
Leukemia mononuclear	16 (30%)	14 (26%)	13 (25%)
Tumor Summary			
Total animals with primary neoplasms[b]	50	45	39
Total primary neoplasms	97	79	74
Total animals with benign neoplasms	43	34	36
Total benign neoplasms	67	53	55
Total animals with malignant neoplasms	26	24	17
Total malignant neoplasms	30	26	19
Total animals with secondary neoplasms[c]	1	1	
Total secondary neoplasms	1	1	

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control

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

+: 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 Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 7 5	1 9 4	2 1 3	2 1 4	2 1 5	2 6 3	2 7 4	1 5 4	1 6 2	1 7 4	1 8 3	1 8 5	1 0 4	2 3 5	2 5 5	2 6 5	1 5 2	1 5 3	2 2 4	2 7 2	2 7 3	2 7 5	2 8 3	2 8 4	2 8 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Neoplastic nodule																										1
Mesentery																								+		4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																										1
Papilloma squamous																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma	X	X	X		X			X	X		X			X			X		X		X		X	X	X	26
Pars distalis, carcinoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Bilateral, C-cell, adenoma									X																	1
C-cell, adenoma															X											5
C-cell, carcinoma																						X				2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adenoma																	X									1
Granulosa cell tumor benign			X																							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	2 1 5	3 4 4	5 2 0	5 2 9	5 5 8	5 6 5	5 9 5	6 2 6	6 3 7	6 5 3	6 7 2	6 7 5	6 9 0	6 9 1	6 9 3	6 9 3	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 2 9	7 3 0	7 3 0
Carcass ID Number	1 9 1	2 4 2	2 3 1	2 5 2	2 3 2	2 0 3	1 9 5	2 2 5	2 3 4	1 8 4	2 6 4	1 7 2	2 8 2	2 4 5	2 4 4	2 5 4	1 5 5	1 6 4	1 7 3	1 9 2	1 9 3	2 0 5	2 3 3	2 4 3	2 5 3	2 6 2	1 6 3	1 6 5
Genital System (continued)																												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal														X														
Endometrium, polyp stromal																												
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, sarcoma	X																											
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Sarcoma	X																											
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																						
Fibroadenoma								X			X	X	X			X	X				X		X			X	X	X
Fibroadenoma, multiple																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																			X									
Subcutaneous tissue, fibrosarcoma							X																					
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																										X		
Carcinoma, early invasion, metastatic, pituitary gland						X																						
Spinal cord					+																							
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Eye																												
Zymbal's gland																												
Carcinoma																												
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																												
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 7 5	1 9 4	2 1 3	2 1 4	2 1 5	2 6 3	2 7 4	1 5 4	1 6 2	1 7 4	1 8 3	1 8 5	2 0 4	2 3 5	2 5 5	2 6 5	1 5 2	1 5 3	2 2 4	2 7 2	2 7 3	2 7 5	2 8 3	2 8 4	2 8 5	**Total Tissues/ Tumors**
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Sarcoma stromal																									1
Endometrium, polyp stromal																X									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mediastinal, sarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Sarcoma																									1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma															X										2
Fibroadenoma	X			X	X	X	X	X	X	X			X		X	X	X	X				X			X	26
Fibroadenoma, multiple		X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Subcutaneous tissue, fibroma																									1
Subcutaneous tissue, fibrosarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant																X									2
Carcinoma, early invasion, metastatic, pituitary gland																									1
Spinal cord																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																									
Eye			+												+	+									3
Zymbal's gland										+															1
Carcinoma										X															1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional epithelium, carcinoma			X																						1
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X										X								X	X					16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg

Number of Days on Study	0 0 3	2 4 3	2 4 3	2 9 9	4 2 7	4 9 4	5 0 4	5 3 5	5 3 9	5 5 0	5 6 8	5 7 5	5 8 4	5 8 8	5 9 6	6 0 0	6 1 0	6 2 4	6 3 0	6 3 7	6 3 9	6 3 9	6 4 4	6 4 4	6 4 7	6 5 2	6 6 2	6 7 2
Carcass ID Number	5 1 1	4 3 1	5 2 1	4 7 1	4 8 2	5 3 2	5 2 2	4 6 1	5 5 1	5 6 1	4 4 3	5 2 3	4 8 4	5 5 4	5 3 5	5 3 4	4 5 5	5 6 2	5 4 5	4 6 3	4 4 4	5 2 4	5 5 2	5 5 3	5 3 3	5 2 5	4 3 5	5 5 5
Alimentary System																												
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X		X							X					X		X			X		X
Pars distalis, carcinoma																							X	X				
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X									X								
General Body System																												
None																												
Genital System																												
Clitoral gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M
Carcinoma																												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant											X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal							X	X																				
Vagina																				+								
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	6 7 4	6 7 7	6 7 9	7 0 2	7 0 6	7 2 5	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 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 0 2	5 0 3	5 1 4	4 3 3	4 6 5	5 4 4	4 7 5	4 9 3	5 4 3	5 6 3	6 6 4	4 3 4	4 5 4	4 8 4	5 1 5	4 4 3	4 6 5	4 6 2	4 6 4	5 0 4	5 1 5	4 8 3	4 9 4	4 9 5	5 0 5	5 6 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	+	M	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma	X				X		X	X				X	X	X		X					X	X	X			19
Pars distalis, carcinoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma																				X						3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Carcinoma									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Granulosa cell tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endometrium, polyp stromal			X		X							X			X							X				7
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	51

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	0 0 3	2 4 3	2 4 3	2 9 9	4 2 7	4 9 4	5 0 4	5 3 5	5 3 9	5 5 0	5 6 8	5 7 5	5 8 4	5 8 8	5 9 6	6 0 0	6 1 0	6 2 4	6 3 0	6 3 7	6 3 9	6 3 9	6 4 4	6 4 4	6 4 7	6 5 2	6 6 2	6 7 2
Carcass ID Number	5 1 1	4 3 1	5 2 1	4 7 1	4 8 2	5 3 2	5 2 2	4 6 1	5 5 1	5 6 1	4 4 3	5 2 3	4 8 4	5 5 4	5 3 5	5 3 4	5 5 5	4 6 2	5 4 5	5 6 3	4 4 4	4 4 4	5 2 4	5 5 2	5 5 3	5 3 3	5 2 5	4 3 5	5 5 5
Integumentary System																													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X					
Fibroadenoma					X	X		X	X					X	X		X					X	X	X				X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																													
Subcutaneous tissue, fibroma																										X			
Subcutaneous tissue, fibrosarcoma																													
Musculoskeletal System																													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																			X										
Carcinoma, early invasion, metastatic, pituitary gland																							X						
Respiratory System																													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																													
Eye		+								+						+													
Zymbal's gland																					+								
Carcinoma																					X								
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
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 Gavage Study of Monochloroacetic Acid: 15 mg/kg (continued)

Number of Days on Study	6 7 4	6 7 7	6 7 9	7 0 2	7 0 6	7 2 5	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 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 0 2	5 0 3	5 1 4	4 3 3	4 6 5	5 4 4	4 7 5	4 9 3	5 4 3	5 6 3	5 6 4	4 3 4	4 5 4	4 8 5	5 1 3	4 4 5	4 6 2	4 6 4	5 0 4	5 1 5	4 8 3	4 9 4	4 9 5	5 0 5	5 6 5	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Carcinoma	X																X									3
Fibroadenoma			X		X	X				X	X	X		X	X				X			X	X		X	23
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma											X															1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Astrocytoma malignant																										1
Carcinoma, early invasion, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																										
Eye																							M		+	4
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Hemangiosarcoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear				X	X							X		X										X	X	14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg

Number of Days on Study	2 5 3	2 5 7	2 7 0	2 8 3	2 9 4	3 3 1	3 4 0	3 5 1	4 5 8	4 9 7	5 1 2	5 3 9	5 6 8	5 8 2	5 9 3	5 9 7	5 9 9	6 1 6	6 4 7	6 6 2	6 7 9	6 8 2	6 8 2	7 0 3	7 1 7	7 2 2	7 2 4	7 2 9
Carcass ID Number	7 8 1	7 8 2	7 6 2	7 2 3	8 2 1	8 0 1	7 3 2	8 0 2	8 3 2	8 2 2	8 0 3	7 8 4	8 1 3	8 1 4	7 7 4	7 4 4	7 2 4	7 1 3	7 4 5	8 0 4	7 5 4	8 1 5	8 3 3	7 4 3	8 0 5	8 2 4	8 3 5	7 2 5
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	I	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																												
Pancreas	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+								+							
Papilloma squamous																					X							
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Carcinoma																												
Parathyroid gland	+	+	+	+	M	+	M	+	M	+	M	M	+	+	+	+	+	+	I	+	+	+	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X		X		X			X	X				X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																												
C-cell, carcinoma																				X								
General Body System																												
None																												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	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 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 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 6 3	7 7 3	8 2 3	8 2 5	8 3 4	7 3 5	7 5 5	7 6 5	7 7 2	7 8 5	7 9 5	8 4 4	7 1 4	7 1 5	7 3 3	7 3 4	7 9 2	8 4 1	8 4 3	8 4 5	7 6 4	7 7 5	7 9 3	7 9 4	8 4 2	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Mesentery													+						+						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Tongue																								+	3
Papilloma squamous																									1
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma						X																			1
Parathyroid gland	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Pars distalis, adenoma	X	X			X				X		X					X				X	X			X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma		X	X																					X	3
C-cell, carcinoma									X																2
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	2 5 3	2 5 7	2 7 0	2 8 3	2 9 4	3 3 1	3 4 0	3 5 1	4 5 8	4 9 7	5 1 2	5 3 9	5 6 8	5 8 2	5 9 3	5 9 7	5 9 9	6 1 6	6 4 7	6 6 2	6 7 9	6 8 2	6 8 2	7 0 3	7 1 7	7 2 2	7 2 4	7 2 9
Carcass ID Number	7 8 1	7 8 2	7 6 2	7 2 3	8 2 1	8 0 1	7 3 2	8 0 2	8 3 2	8 2 2	8 0 3	7 8 4	8 1 3	8 1 4	7 7 4	7 4 4	7 2 4	7 1 3	7 4 5	8 0 4	7 5 4	8 1 5	8 3 3	7 4 3	8 0 5	8 2 4	8 3 5	7 2 5
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Sarcoma																		X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal											X						X		X			X		X				
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	I
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X						
Fibroadenoma									X				X	X					X	X			X			X		X
Fibroadenoma, multiple																					X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Keratoacanthoma																												
Subcutaneous tissue, fibroma																												
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	A	+	+	+	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																												
Eye																												+
Harderian gland											+																	
Urinary System																												
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+
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 Gavage Study of Monochloroacetic Acid: 30 mg/kg (continued)

Number of Days on Study	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 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 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 6 3	7 7 3	8 2 3	8 2 5	8 3 4	7 3 5	7 5 5	7 6 5	7 7 2	7 8 5	7 9 5	8 4 4	7 1 4	7 1 5	7 3 3	7 3 4	7 3 9	8 4 2	8 4 1	8 4 3	8 4 5	7 6 4	7 7 5	7 9 3	7 9 4	8 4 2	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Endometrium, polyp stromal		X	X		X								X													9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Thymus	+	+	+	I	M	+	+	+	+	+	I	+	+	+	+	M	+	+	+	M	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma																	X									2
Fibroadenoma	X			X	X	X	X	X	X			X			X			X	X					X		21
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Keratoacanthoma											X															1
Subcutaneous tissue, fibroma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Special Senses System																										
Eye																			+							2
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear		X																X		X	X			X		13

TABLE B3
Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Mammary Gland: Fibroadenoma			
Overall rates[a]	27/53 (51%)	23/53 (43%)	22/53 (42%)
Adjusted rates[b]	64.1%	66.3%	63.4%
Terminal rates[c]	22/37 (59%)	9/19 (47%)	14/26 (54%)
First incidence (days)	626	427	458
Life table tests[d]	P=0.323	P=0.070	P=0.367
Logistic regression tests[d]	P=0.439N	P=0.559N	P=0.545N
Cochran-Armitage test[d]	P=0.190N		
Fisher exact test[d]		P=0.280N	P=0.218N
Mammary Gland: Carcinoma			
Overall rates	2/53 (4%)	3/53 (6%)	2/53 (4%)
Adjusted rates	4.7%	12.0%	6.9%
Terminal rates	1/37 (3%)	1/19 (5%)	1/26 (4%)
First incidence (days)	565	644	682
Life table tests	P=0.461	P=0.301	P=0.590
Logistic regression tests	P=0.543	P=0.474	P=0.671
Cochran-Armitage test	P=0.594		
Fisher exact test		P=0.500	P=0.691N
Mammary Gland: Fibroadenoma or Carcinoma			
Overall rates	28/53 (53%)	25/53 (47%)	24/53 (45%)
Adjusted rates	64.8%	70.9%	67.5%
Terminal rates	22/37 (59%)	10/19 (53%)	15/26 (58%)
First incidence (days)	565	427	458
Life table tests	P=0.243	P=0.043	P=0.281
Logistic regression tests	P=0.535N	P=0.531	P=0.540
Cochran-Armitage test	P=0.248N		
Fisher exact test		P=0.349N	P=0.280N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	26/53 (49%)	19/53 (36%)	17/53 (32%)
Adjusted rates	63.2%	61.7%	48.7%
Terminal rates	22/37 (59%)	9/19 (47%)	9/26 (35%)
First incidence (days)	637	299	539
Life table tests	P=0.405N	P=0.197	P=0.409N
Logistic regression tests	P=0.144N	P=0.330N	P=0.201N
Cochran-Armitage test	P=0.045N		
Fisher exact test		P=0.119N	P=0.057N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	28/53 (53%)	21/53 (40%)	17/53 (32%)
Adjusted rates	66.3%	64.2%	48.7%
Terminal rates	23/37 (62%)	9/19 (47%)	9/26 (35%)
First incidence (days)	565	299	539
Life table tests	P=0.302N	P=0.172	P=0.290N
Logistic regression tests	P=0.071N	P=0.312N	P=0.104N
Cochran-Armitage test	P=0.019N		
Fisher exact test		P=0.121N	P=0.024N

TABLE B3
Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Thyroid Gland (C-Cell): Adenoma			
Overall rates	6/53 (11%)	3/52 (6%)	3/52 (6%)
Adjusted rates	14.1%	10.2%	11.5%
Terminal rates	3/37 (8%)	1/19 (5%)	3/26 (12%)
First incidence (days)	558	568	729 (T)
Life table tests	P=0.344N	P=0.497N	P=0.420N
Logistic regression tests	P=0.235N	P=0.264N	P=0.319N
Cochran-Armitage test	P=0.187N		
Fisher exact test		P=0.254N	P=0.254N
Thyroid Gland (C-Cell): Adenoma or Carcinoma			
Overall rates	8/53 (15%)	3/52 (6%)	5/52 (10%)
Adjusted rates	19.2%	10.2%	17.9%
Terminal rates	5/37 (14%)	1/19 (5%)	4/26 (15%)
First incidence (days)	558	568	662
Life table tests	P=0.419N	P=0.329N	P=0.507N
Logistic regression tests	P=0.299N	P=0.130N	P=0.391N
Cochran-Armitage test	P=0.220N		
Fisher exact test		P=0.107N	P=0.290N
Uterus: Stromal Polyp			
Overall rates	1/53 (2%)	7/53 (13%)	9/53 (17%)
Adjusted rates	2.7%	26.6%	26.8%
Terminal rates	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	729 (T)	504	512
Life table tests	P=0.004	P=0.005	P=0.003
Logistic regression tests	P=0.006	P=0.024	P=0.006
Cochran-Armitage test	P=0.009		
Fisher exact test		P=0.030	P=0.008
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	2/53 (4%)	7/53 (13%)	9/53 (17%)
Adjusted rates	5.1%	26.6%	26.8%
Terminal rates	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	691	504	512
Life table tests	P=0.009	P=0.015	P=0.010
Logistic regression tests	P=0.015	P=0.062	P=0.018
Cochran-Armitage test	P=0.023		
Fisher exact test		P=0.080	P=0.026
Uterus: Stromal Polyp or Stromal Sarcoma[e]			
Overall rates	3/60 (5%)	7/57 (12%)	10/60 (17%)
Adjusted rates	6.8%	26.6%	28.3%
Interim sacrifice 1	1/7 (14%)	0/4 (0%)	1/7 (14%)
Terminal rates	1/37 (3%)	3/19 (16%)	4/26 (15%)
First incidence (days)	456 (I)	504	456 (I)
Life table tests	P=0.013	P=0.034	P=0.016
Logistic regression tests	P=0.022	P=0.125	P=0.031
Cochran-Armitage test	P=0.030		
Fisher exact test		P=0.141	P=0.037

TABLE B3
Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	15 mg/kg	30 mg/kg
All Organs: Mononuclear Leukemia			
Overall rates	16/53 (30%)	14/53 (26%)	13/53 (25%)
Adjusted rates	33.5%	42.2%	36.2%
Terminal rates	6/37 (16%)	4/19 (21%)	5/26 (19%)
First incidence (days)	520	504	539
Life table tests	P=0.447	P=0.254	P=0.501
Logistic regression tests	P=0.354N	P=0.419N	P=0.393N
Cochran-Armitage test	P=0.292N		
Fisher exact test		P=0.415N	P=0.332N
All Organs: Benign Tumors			
Overall rates	43/53 (81%)	34/53 (64%)	36/53 (68%)
Adjusted rates	93.4%	85.8%	87.6%
Terminal rates	34/37 (92%)	14/19 (74%)	21/26 (81%)
First incidence (days)	558	299	458
Life table tests	P=0.204	P=0.045	P=0.218
Logistic regression tests	P=0.357N	P=0.168N	P=0.526N
Cochran-Armitage test	P=0.082N		
Fisher exact test		P=0.040N	P=0.090N
All Organs: Malignant Tumors			
Overall rates	26/53 (49%)	24/53 (45%)	17/53 (32%)
Adjusted rates	51.6%	65.7%	47.0%
Terminal rates	13/37 (35%)	8/19 (42%)	8/26 (31%)
First incidence (days)	215	504	539
Life table tests	P=0.398N	P=0.094	P=0.372N
Logistic regression tests	P=0.082N	P=0.463N	P=0.080N
Cochran-Armitage test	P=0.047N		
Fisher exact test		P=0.423N	P=0.057N
All Organs: Benign and Malignant Tumors			
Overall rates	50/53 (94%)	45/53 (85%)	39/53 (74%)
Adjusted rates	96.2%	93.6%	92.8%
Terminal rates	35/37 (95%)	16/19 (84%)	23/26 (88%)
First incidence (days)	215	299	458
Life table tests	P=0.332	P=0.007	P=0.401
Logistic regression tests	P=0.020N	P=0.253N	P=0.047N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.101N	P=0.003N

(T)Terminal sacrifice
(I)Interim sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Includes 15-month interim sacrifice animals

TABLE B4
Historical Incidence of Uterine Stromal Polyps and Stromal Sarcomas in Female F344/N Rats Receiving Water Vehicle by Gavage

	Incidence in Controls		
	Endometrial Stromal Polyp	Endometrial Stromal Sarcoma	Endometrial Stromal Polyp or Endometrial Stromal Sarcoma
Overall Historical Incidence[a]			
Total	116/562 (20.6%)[b]	2/562 (0.4%)	118/562 (21.0%)[b,c]
Standard deviation	7.6%	0.8%	7.9%
Range	10%-38%	0%-2%	10%-38%

[a] Data as of 22 December 1989 for 2-year studies on the Toxicology Data Management System, and as of 6 March 1990 for 2-year studies on the Carcinogenesis Bioassay Data System. No historical control data were available for water gavage studies conducted at the International Research and Development Corporation.
[b] Includes one (1) cervical endometrial stromal polyp.
[c] Includes one (1) cervical endometrial stromal sarcoma.

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Disposition Summary			
Animals initially in study	70	70	70
Scheduled sacrifice	17	17	17
Early deaths			
Moribund	14	21	13
Dead	2	11	13
Accidental deaths	0	2	1
Survivors			
Terminal sacrifice	37	19	25
Moribund	0	0	1
Animals examined microscopically	53	53	53
Alimentary System			
Esophagus	(53)	(52)	(52)
Inflammation, acute, focal			1 (2%)
Intestine large, cecum	(53)	(53)	(51)
Autolysis		3 (6%)	
Parasite metazoan		1 (2%)	
Intestine large, colon	(53)	(53)	(51)
Autolysis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Parasite metazoan	8 (15%)	3 (6%)	6 (12%)
Intestine large, rectum	(52)	(53)	(50)
Hyperplasia, lymphoid			1 (2%)
Parasite metazoan	2 (4%)	1 (2%)	3 (6%)
Submucosa, inflammation, acute, focal			1 (2%)
Intestine small, duodenum	(53)	(51)	(51)
Autolysis		1 (2%)	
Intestine small, ileum	(53)	(53)	(48)
Autolysis		3 (6%)	
Congestion		2 (4%)	
Edema		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Parasite metazoan		1 (2%)	
Intestine small, jejunum	(53)	(52)	(49)
Autolysis		3 (6%)	
Liver	(53)	(53)	(53)
Angiectasis	1 (2%)		
Angiectasis, focal	1 (2%)		1 (2%)
Basophilic focus	16 (30%)	6 (11%)	16 (30%)
Basophilic focus, multiple	21 (40%)	17 (32%)	14 (26%)
Congestion	1 (2%)	2 (4%)	1 (2%)
Cytoplasmic alteration, focal	6 (11%)	3 (6%)	4 (8%)
Degeneration, fatty	1 (2%)	1 (2%)	
Hemorrhage, focal	1 (2%)		
Hepatodiaphragmatic nodule	4 (8%)	1 (2%)	3 (6%)
Inflammation, acute, focal	2 (4%)		2 (4%)
Inflammation, granulomatous, multifocal	21 (40%)	19 (36%)	18 (34%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Alimentary System (continued)			
Liver (continued)			
Necrosis, acute, focal		2 (4%)	1 (2%)
Necrosis, coagulative, acute, multifocal	1 (2%)		
Vacuolization cytoplasmic, focal	1 (2%)	1 (2%)	
Bile duct, hyperplasia	7 (13%)	1 (2%)	3 (6%)
Hepatocyte, hypertrophy, focal	1 (2%)		
Mesentery	(4)		(2)
Inflammation, chronic, multifocal	1 (25%)		1 (50%)
Fat, necrosis, focal	3 (75%)		2 (100%)
Pancreas	(53)	(53)	(51)
Atrophy, focal	19 (36%)	15 (28%)	10 (20%)
Cytoplasmic alteration, focal		1 (2%)	
Inflammation, chronic, focal	1 (2%)		
Acinus, hyperplasia			1 (2%)
Salivary glands	(53)	(53)	(53)
Atrophy, focal			1 (2%)
Hemorrhage	1 (2%)		
Hyperplasia, focal		1 (2%)	
Infiltration cellular, lymphocytic, multifocal			2 (4%)
Inflammation, chronic			1 (2%)
Duct, inflammation, chronic	5 (9%)		2 (4%)
Duct, inflammation, chronic active	8 (15%)		7 (13%)
Stomach, forestomach	(51)	(52)	(53)
Inflammation, acute	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	
Ulcer			1 (2%)
Epithelium, hyperplasia	6 (12%)	4 (8%)	4 (8%)
Muscularis, hypertrophy, focal			1 (2%)
Submucosa, inflammation, acute			1 (2%)
Stomach, glandular	(53)	(53)	(53)
Infiltration cellular, lymphocytic, focal			1 (2%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		
Necrosis, acute	1 (2%)	4 (8%)	3 (6%)
Pigmentation, focal		1 (2%)	
Arteriole, submucosa, thrombus			1 (2%)
Serosa, inflammation, chronic, multifocal			1 (2%)
Submucosa, inflammation, chronic			1 (2%)
Cardiovascular System			
Heart	(53)	(53)	(53)
Inflammation, chronic	41 (77%)	31 (58%)	36 (68%)
Atrium left, thrombus	1 (2%)	2 (4%)	
Coronary artery, inflammation, chronic			1 (2%)
Pericardium, fibrosis, focal			1 (2%)
Valve, thrombus			1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Endocrine System			
Adrenal gland, cortex	(53)	(53)	(52)
Angiectasis, focal			1 (2%)
Congestion	1 (2%)	1 (2%)	2 (4%)
Ectasia	2 (4%)		
Hemorrhage		2 (4%)	1 (2%)
Hyperplasia, focal	10 (19%)	8 (15%)	12 (23%)
Hypertrophy	1 (2%)		
Hypertrophy, focal	9 (17%)	4 (8%)	4 (8%)
Mineralization		1 (2%)	
Necrosis, acute, focal		1 (2%)	
Thrombus		1 (2%)	
Vacuolization cytoplasmic, diffuse		2 (4%)	
Vacuolization cytoplasmic, focal	11 (21%)	9 (17%)	6 (12%)
Bilateral, hyperplasia, focal		1 (2%)	
Adrenal gland, medulla	(52)	(52)	(53)
Hyperplasia, focal	4 (8%)		4 (8%)
Islets, pancreatic	(53)	(53)	(51)
Hyperplasia		1 (2%)	
Parathyroid gland	(43)	(43)	(42)
Congestion, focal			1 (2%)
Hyperplasia	1 (2%)		
Pituitary gland	(53)	(53)	(53)
Autolysis			1 (2%)
Congestion, focal			1 (2%)
Hemorrhage			2 (4%)
Pigmentation, focal	1 (2%)		
Pars distalis, angiectasis	6 (11%)	4 (8%)	5 (9%)
Pars distalis, cyst	10 (19%)	4 (8%)	7 (13%)
Pars distalis, ectasia			1 (2%)
Pars distalis, hyperplasia	9 (17%)	12 (23%)	13 (25%)
Pars distalis, vacuolization nuclear			1 (2%)
Thyroid gland	(53)	(52)	(52)
Ultimobranchial cyst		1 (2%)	1 (2%)
C-cell, hyperplasia	20 (38%)	8 (15%)	16 (31%)
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia			1 (2%)
General Body System			
None			
Genital System			
Clitoral gland	(44)	(45)	(48)
Hyperplasia		1 (2%)	1 (2%)
Hyperplasia, squamous		1 (2%)	
Inflammation, acute	5 (11%)	8 (18%)	4 (8%)
Inflammation, chronic	11 (25%)	6 (13%)	12 (25%)
Inflammation, chronic active	6 (14%)	1 (2%)	5 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Genital System (continued)			
Ovary	(53)	(53)	(53)
Atrophy			1 (2%)
Hemorrhage	1 (2%)		
Follicle, cyst	6 (11%)	2 (4%)	5 (9%)
Periovarian tissue, cyst	1 (2%)		1 (2%)
Uterus	(53)	(53)	(53)
Dilatation	2 (4%)	5 (9%)	3 (6%)
Hemorrhage			1 (2%)
Inflammation, acute	2 (4%)		
Inflammation, chronic	1 (2%)		
Endometrium, fibrosis			1 (2%)
Endometrium, hyperplasia, cystic	1 (2%)	2 (4%)	
Vagina		(1)	
Inflammation, acute		1 (100%)	
Hematopoietic System			
Bone marrow	(53)	(53)	(53)
Hyperplasia	1 (2%)	1 (2%)	
Hypoplasia	1 (2%)		
Myelofibrosis	2 (4%)	3 (6%)	
Pigmentation	1 (2%)		
Myeloid cell, hyperplasia		4 (8%)	
Lymph node	(53)	(52)	(53)
Mediastinal, congestion			2 (4%)
Renal, congestion		1 (2%)	
Renal, hemorrhage		1 (2%)	
Lymph node, mesenteric	(52)	(52)	(53)
Congestion			1 (2%)
Edema	1 (2%)		
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Lymphocyte, depletion			1 (2%)
Spleen	(53)	(53)	(53)
Angiectasis		1 (2%)	
Fibrosis	1 (2%)		1 (2%)
Hematopoietic cell proliferation			
granulocytic	2 (4%)	5 (9%)	
Inflammation, granulomatous, focal		1 (2%)	
Necrosis, focal		1 (2%)	
Pigmentation	3 (6%)	1 (2%)	4 (8%)
Capsule, fibrosis, multifocal			1 (2%)
Thymus	(51)	(51)	(44)
Autolysis	1 (2%)		
Cyst	2 (4%)		1 (2%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)
Medulla, hyperplasia, focal			1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Integumentary System			
Mammary gland	(53)	(53)	(51)
Galactocele	5 (9%)		5 (10%)
Hyperplasia	23 (43%)		22 (43%)
Hyperplasia, cystic		1 (2%)	
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic active, multifocal			1 (2%)
Duct, ectasia	23 (43%)	11 (21%)	2 (4%)
Skin	(53)	(52)	(52)
Face, inflammation, acute		1 (2%)	
Face, inflammation, chronic active, focal			1 (2%)
Subcutaneous tissue, hemorrhage	1 (2%)		
Musculoskeletal System			
Bone	(53)	(53)	(53)
Hyperostosis			1 (2%)
Osteopetrosis	1 (2%)		
Nervous System			
Brain	(53)	(53)	(53)
Congestion			2 (4%)
Hemorrhage, focal		1 (2%)	
Hydrocephalus	1 (2%)		
Inflammation, acute, focal		1 (2%)	
Inflammation, chronic, focal		1 (2%)	
Cerebellum, cyst			1 (2%)
Third ventricle, dilatation	1 (2%)		
Respiratory System			
Lung	(53)	(53)	(53)
Congestion	1 (2%)	6 (11%)	13 (25%)
Fibrosis, focal		1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	3 (6%)
Inflammation, granulomatous, multifocal			1 (2%)
Alveolar epithelium, hyperplasia, focal		1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocytic	3 (6%)	3 (6%)	2 (4%)
Interstitium, infiltration cellular, multifocal	1 (2%)		
Perivascular, inflammation, chronic	14 (26%)		12 (23%)
Nose	(52)	(53)	(48)
Autolysis		4 (8%)	
Foreign body		1 (2%)	1 (2%)
Fungus	5 (10%)	1 (2%)	1 (2%)
Hemorrhage		3 (6%)	
Inflammation, chronic, focal	1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Respiratory System (continued)			
Nose (continued)			
Mucosa, inflammation, acute		6 (11%)	5 (10%)
Mucosa, inflammation, chronic active	5 (10%)	2 (4%)	1 (2%)
Nasolacrimal duct, cyst		1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, acute	4 (8%)	1 (2%)	6 (13%)
Nasolacrimal duct, inflammation, chronic			4 (8%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)
Sinus, inflammation, acute		1 (2%)	1 (2%)
Vein, thrombus		1 (2%)	
Trachea	(53)	(53)	(53)
Inflammation, chronic			2 (4%)
Special Senses System			
Eye	(3)	(4)	(2)
Bilateral, lens, cataract		1 (25%)	
Lens, cataract	2 (67%)	2 (50%)	2 (100%)
Retina, degeneration	3 (100%)	1 (25%)	2 (100%)
Sclera, mineralization, focal			1 (50%)
Harderian gland			(1)
Inflammation, chronic			1 (100%)
Urinary System			
Kidney	(53)	(53)	(52)
Autolysis		7 (13%)	1 (2%)
Congestion		3 (6%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, suppurative, multifocal			1 (2%)
Mineralization, focal		2 (4%)	
Mineralization, multifocal	9 (17%)	2 (4%)	15 (29%)
Nephropathy	46 (87%)	38 (72%)	35 (67%)
Cortex, renal tubule, necrosis			1 (2%)
Cortex, renal tubule, necrosis, focal		1 (2%)	
Renal tubule, epithelium, pigmentation	3 (6%)	4 (8%)	2 (4%)
Urinary bladder	(52)	(52)	(49)
Calculus micro observation only, multifocal	1 (2%)		
Hemorrhage, focal			1 (2%)
Hyperplasia, papillary	1 (2%)		
Infiltration cellular, lymphocytic		1 (2%)	
Transitional epithelium, hyperplasia		1 (2%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF MONOCHLOROACETIC ACID

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	7	11	26
Moribund	5	10	8
Accidental deaths	2	0	5
Survivors			
Terminal sacrifice	46	39	21
Animals examined microscopically	60	60	60
Alimentary System			
Esophagus	(59)	(60)	(60)
Intestine large, rectum	(58)	(58)	(50)
Adenocarcinoma		1 (2%)	
Intestine small, jejunum	(53)	(56)	(40)
Liver	(60)	(59)	(59)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Hemangioma	2 (3%)		
Hemangiosarcoma		1 (2%)	1 (2%)
Hepatocellular carcinoma	6 (10%)	2 (3%)	5 (8%)
Hepatocellular adenoma	6 (10%)	6 (10%)	1 (2%)
Mesentery	(4)	(1)	
Sarcoma, metastatic, skin	1 (25%)		
Pancreas	(58)	(59)	(57)
Pharynx	(1)		
Palate, mast cell tumor malignant	1 (100%)		
Stomach, glandular	(58)	(59)	(54)
Carcinoma, metastatic, uncertain primary site	1 (2%)		
Tooth	(5)	(2)	(2)
Peridontal tissue, mast cell tumor malignant	1 (20%)		
Cardiovascular System			
Blood vessel	(58)	(58)	(59)
Fibrosarcoma, metastatic, skin		1 (2%)	
Heart	(60)	(59)	(60)
Fibrosarcoma, metastatic, skin		1 (2%)	
Hemangioma		1 (2%)	
Endocrine System			
Adrenal gland, cortex	(60)	(59)	(60)
Adenoma		1 (2%)	
Carcinoma		1 (2%)	
Subcapsular, adenoma	2 (3%)	1 (2%)	2 (3%)
Adrenal gland, medulla	(59)	(59)	(60)
Pheochromocytoma benign		1 (2%)	1 (2%)
Thyroid gland	(60)	(58)	(57)
Follicular cell, adenoma	1 (2%)		
Follicular cell, carcinoma	1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
General Body System			
None			
Genital System			
Preputial gland	(8)	(6)	(8)
Sarcoma, metastatic, skin	1 (13%)		
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Lymph node	(58)	(55)	(51)
Mediastinal, fibrosarcoma, metastatic, skin		1 (2%)	
Pancreatic, carcinoma, metastatic, uncertain primary site	1 (2%)		
Lymph node, mesenteric	(56)	(55)	(50)
Hemangiosarcoma	1 (2%)		
Sarcoma, metastatic, skin	1 (2%)		
Spleen	(59)	(58)	(60)
Hemangioma	1 (2%)		
Thymus	(49)	(42)	(38)
Integumentary System			
Skin	(60)	(60)	(59)
Fibrosarcoma		4 (7%)	3 (5%)
Fibrosarcoma, multiple	1 (2%)		
Neurofibrosarcoma			2 (3%)
Sarcoma	1 (2%)		1 (2%)
Musculoskeletal System			
Skeletal muscle	(1)	(1)	(1)
Fibrosarcoma, metastatic			1 (100%)
Thoracic, fibrosarcoma, metastatic, skin		1 (100%)	
Nervous System			
Brain	(60)	(58)	(60)
Respiratory System			
Lung	(60)	(59)	(60)
Alveolar/bronchiolar adenoma	6 (10%)	10 (17%)	4 (7%)
Alveolar/bronchiolar adenoma, multiple	3 (5%)		1 (2%)
Alveolar/bronchiolar carcinoma	4 (7%)		
Fibrosarcoma, metastatic, skin		2 (3%)	1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (3%)	1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)		
Nose	(60)	(59)	(60)
Trachea	(60)	(59)	(60)
Fibrosarcoma, metastatic, skin		2 (3%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Special Senses System			
Harderian gland	(3)	(3)	(2)
Adenoma	2 (67%)	3 (100%)	2 (100%)
Urinary System			
Kidney	(60)	(59)	(60)
Sarcoma, metastatic, skin	1 (2%)		
Urinary bladder	(57)	(58)	(54)
Systemic Lesions			
Multiple organs[a]	(60)	(60)	(60)
Lymphoma malignant mixed	8 (13%)	7 (12%)	5 (8%)
Tumor Summary			
Total animals with primary neoplasms[b]	31	32	21
Total primary neoplasms	47	39	28
Total animals with benign neoplasms	20	21	11
Total benign neoplasms	23	23	11
Total animals with malignant neoplasms	20	14	13
Total malignant neoplasms	24	16	17
Total animals with secondary neoplasms[c]	5	3	2
Total secondary neoplasms	10	9	2
Total animals with malignant neoplasms uncertain primary site	2		

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control

Number of Days on Study	0 5 9	1 5 7	3 6 1	4 5 5	5 1 7	5 6 6	6 2 7	6 3 7	6 3 9	6 5 2	6 5 7	6 8 9	7 0 2	7 1 6	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 2 9	7 2 9
Carcass ID Number	0 5 1	1 1 1	0 7 1	0 3 1	0 8 1	0 4 3	0 7 2	1 0 3	0 2 2	0 6 1	0 9 2	0 8 5	0 5 5	1 1 4	0 1 1	0 1 3	0 4 1	0 4 2	0 6 2	0 6 5	0 8 3	0 8 4	0 9 1	0 9 3	0 9 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Gallbladder	+	+	A	A	A	+	A	A	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	A	+	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	A	+	A	A	A	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																									
Hemangioma																					X			X	
Hepatocellular carcinoma					X			X	X									X							
Hepatocellular adenoma													X						X		X				
Mesentery								+			+														
Sarcoma, metastatic, skin											X														
Pancreas	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																					+				
Palate, mast cell tumor malignant																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																									
Tooth																			+		+				
Peridontal tissue, mast cell tumor malignant																					X				
Cardiovascular System																									
Blood vessel	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731
Carcass ID Number	10013	10133	10122	10233	10125	10212	10024	10225	10333	10335	10044	10455	10052	10233	10553	10663	10755	10822	11122	11225	11214	11451	11521	12101	12233	12032
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																										
Hemangioma																										
Hepatocellular carcinoma																									X	
Hepatocellular adenoma							X		X	X																
Mesentery											+											+				
Sarcoma, metastatic, skin																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																										
Palate, mast cell tumor malignant																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																										
Tooth							+	+																		
Peridontal tissue, mast cell tumor malignant																										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	0 3 4	0 5 4	0 6 4	0 7 3	0 7 4	0 9 5	1 0 2	1 0 4	1 0 5	1 2 4	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Gallbladder	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	55
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	54
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, uncertain primary site			X								1
Hemangioma											2
Hepatocellular carcinoma							X				6
Hepatocellular adenoma											6
Mesentery											4
Sarcoma, metastatic, skin											1
Pancreas	+	+	+	+	+	+	+	+	+	+	58
Pharynx											1
Palate, mast cell tumor malignant											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
Carcinoma, metastatic, uncertain primary site			X								1
Tooth					+						5
Peridontal tissue, mast cell tumor malignant											1
Cardiovascular System											
Blood vessel	+		+	+	+	+	+	+	+	+	58
Heart	+	+	+	+	+	+	+	+	+	+	60

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	0 5 9	1 5 7	3 6 1	4 5 5	5 1 7	5 6 6	6 2 7	6 3 7	6 3 9	6 5 2	6 5 7	6 8 9	7 0 2	7 1 6	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 2 9	7 2 9
Carcass ID Number	0 5 1	1 1 1	0 7 1	0 3 1	0 8 1	0 4 3	0 7 2	1 0 3	0 2 2	0 6 1	0 9 2	0 8 5	0 5 5	1 1 4	0 1 1	0 1 3	0 4 1	0 4 2	0 6 2	0 6 5	0 8 3	0 8 4	0 9 1	0 9 3	0 9 4
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	M	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	M	I	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+									+							+
Preputial gland		+				+					+	+	+					+							
Sarcoma, metastatic, skin											X														
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+			+	+									+											
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, carcinoma, metastatic, uncertain primary site																									
Lymph node, mesenteric	+	I	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Sarcoma, metastatic, skin											X														
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	M	+	+	+	+	I	M	M	+	M	I	+	M	M	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	+	M	M	M	M	M	+	M	+	+	+	M	+	I	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, multiple																									
Sarcoma											X														

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731
Carcass ID Number	10113	10132	10223	10235	10252	10124	10245	10255	10333	10355	10444	10455	10522	10553	10633	10755	10822	11122	11255	11214	10045	10151	10451	10232
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	M	+	M	+	+	+	M	+	M	+	+	+	M	+	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
Follicular cell, carcinoma																	X							
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis			+	+							+													
Preputial gland				+																				
Sarcoma, metastatic, skin																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic, carcinoma, metastatic, uncertain primary site																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Sarcoma, metastatic, skin																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																	X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, multiple																								
Sarcoma																								

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	0 3 4	0 5 4	0 6 4	0 7 3	0 7 4	0 9 5	1 0 2	1 0 4	1 0 5	1 2 4	**Total Tissues/ Tumors**
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma		X		X							2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	56
Parathyroid gland	+	M	M	+	M	+	+	+	+	+	41
Pituitary gland	+	+	M	+	+	+	+	+	+	+	56
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma											1
Follicular cell, carcinoma											1
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis			+				+		+		9
Preputial gland										+	8
Sarcoma, metastatic, skin											1
Prostate	+	+	+	+	+	+	+	+	+	+	59
Seminal vesicle									+		5
Testes	+	+	+	+	+	+	+	+	+	+	60
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	58
Pancreatic, carcinoma, metastatic, uncertain primary site			X								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	56
Hemangiosarcoma											1
Sarcoma, metastatic, skin											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangioma											1
Thymus	+	+	+	+	+	+	+	+	+	M	49
Integumentary System											
Mammary gland	M	M	M	+	M	+	+	M	M	+	13
Skin	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma, multiple					X						1
Sarcoma											1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	0 5 9	1 5 7	3 6 1	4 5 5	5 1 7	5 6 6	6 2 7	6 3 7	6 3 9	6 5 2	6 5 7	6 8 9	7 0 2	7 1 6	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 2 9	7 2 9	7 2 9
Carcass ID Number	0 5 1	1 1 1	0 7 1	0 3 1	0 8 1	0 4 3	0 7 2	1 0 3	0 2 2	0 6 1	0 9 2	0 8 5	0 5 5	1 1 4	0 1 1	1 1 3	0 4 1	0 4 2	0 6 2	0 6 5	0 8 3	0 8 4	0 9 1	0 9 3	0 9 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																							X		
Alveolar/bronchiolar carcinoma																					X			X	
Hepatocellular carcinoma, metastatic, liver					X				X																
Sarcoma, metastatic, uncertain primary site							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin											X														
Urinary bladder	+	+	A	+	+	I	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed								X		X			X												

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	730	000	000	000	000	000	000	000	000	000	000	000	000	000	000	000	011	011	011	011	031
Carcass ID Number	10121	11323	12232	12353	12355	10122	12424	12255	13335	13355	14444	14555	15252	15323	16633	17555	18222	11122	11255	12141	10145	00511	01132	02232	03332
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X								X		X									
Alveolar/bronchiolar adenoma, multiple						X																				
Alveolar/bronchiolar carcinoma			X				X																			
Hepatocellular carcinoma, metastatic, liver																										
Sarcoma, metastatic, uncertain primary site																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland				+		+								+												
Adenoma				X										X												
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed			X			X		X								X										

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	0 3 4	0 5 4	0 6 4	0 7 3	0 7 4	0 9 5	1 0 2	1 0 4	1 0 5	1 2 4	**Total Tissues/ Tumors**
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Spinal cord											1
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma	X		X				X				6
Alveolar/bronchiolar adenoma, multiple				X							3
Alveolar/bronchiolar carcinoma											4
Hepatocellular carcinoma, metastatic, liver											2
Sarcoma, metastatic, uncertain primary site											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Harderian gland											3
Adenoma											2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Sarcoma, metastatic, skin											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	57
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed			X								8

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg

Number of Days on Study	0 0 0 0 0 1 1 4 5 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 0 0 1 6 6 2 3 3 4 6 7 8 1 3 5 7 7 7 8 1 1 2 2 2 2 6 6 1 6 6 6 6 4 2 6 3 1 4 9 9 0 3 4 7 4 6 9 9 9 9
Carcass ID Number	2 3 3 2 3 2 3 3 3 2 3 2 2 3 2 2 3 3 3 3 2 2 2 2 2 5 3 1 7 1 5 2 6 1 7 6 9 8 6 6 7 0 0 1 2 8 6 6 8 9 1 1 1 1 2 2 1 1 3 3 4 5 4 5 2 5 2 3 5 5 5 3 4 2 3
Alimentary System	
Esophagus	+ +
Gallbladder	+ M + + A + + + A + + A A A + M + + + + + + + + +
Intestine large	+ A + + + + + + + + + + + + A + + + + + + + + + +
Intestine large, cecum	+ A + + A + + + + + + + A + A + + + + + + + + +
Intestine large, colon	+ A + + + + + + + + + + + + A + + + + + + + + +
Intestine large, rectum	+ A + + + + + + + + + + + + A + + + + + + + + +
Adenocarcinoma	X
Intestine small	+ M + + A + A + + + + + + A + + + + + + + + + + +
Intestine small, duodenum	+ M A + A + A + + + + + + A A A + + + + + + + + +
Intestine small, ileum	+ M + + A + A + A + + + + A + A + + + + + + + + +
Intestine small, jejunum	+ M + + A + A + + + + + + A + + + + + + + + + + +
Liver	+ M +
Hemangiosarcoma	
Hepatocellular carcinoma	X
Hepatocellular adenoma	X X
Mesentery	
Pancreas	+ M +
Salivary glands	M M + + + + + + + + + + + M + + + + + + + + + + +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ I +
Tooth	+
Cardiovascular System	
Blood vessel	+ M + + + + + + M + + + + + + + + + + + + + + + +
Fibrosarcoma, metastatic, skin	X
Heart	+ M +
Fibrosarcoma, metastatic, skin	X
Hemangioma	X
Endocrine System	
Adrenal gland	+ M +
Adrenal gland, cortex	+ M +
Adenoma	
Carcinoma	
Subcapsular, adenoma	
Adrenal gland, medulla	+ M +
Pheochromocytoma benign	
Islets, pancreatic	+ M +
Parathyroid gland	M M M M + + M + M + M M M + M M M + M M + + + M M
Pituitary gland	+ M + + + + + + + M + + + + + + + + + + + + + I
Thyroid gland	M M +
General Body System	
None	

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731
Carcass ID Number	29 4	30 1	30 4	33 2	33 5	34 1	35 2	55 3	63 3	65 3	25 4	25 5	27 2	28 1	29 1	30 5	31 4	32 4	33 4	34 2	44 4	46 2	26 1	26 5	27 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Hepatocellular carcinoma																		X							
Hepatocellular adenoma			X																		X				
Mesentery																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+																		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Hemangioma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Carcinoma											X														
Subcapsular, adenoma												X													
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	M	M	M	+	M	M	+	+	+	M	M	M	M	M	+	M	M	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	2 8 3	2 9 2	3 2 2	3 2 3	3 3 3	3 4 3	3 4 5	3 5 1	3 5 4	3 5 5	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	I	+	+	52
Intestine large	+	+	+	+	+	+	+	+	+	+	58
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	55
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma											1
Intestine small	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	54
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	56
Liver	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Hepatocellular carcinoma											2
Hepatocellular adenoma							X			X	6
Mesentery											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Salivary glands	+	+	+	+	+	+	+	+	+	+	57
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tooth											2
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	58
Fibrosarcoma, metastatic, skin											1
Heart	+	+	+	+	+	+	+	+	+	+	59
Fibrosarcoma, metastatic, skin											1
Hemangioma											1
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Carcinoma											1
Subcapsular, adenoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Pheochromocytoma benign					X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	M	M	M	M	+	M	M	I	M	M	19
Pituitary gland	+	+	+	+	+	+	+	+	+	+	57
Thyroid gland	+	+	+	+	+	+	+	+	+	+	58
General Body System											
None											

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	0 0 0 0 0 1 1 4 5 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 0 0 1 6 6 2 3 3 4 6 7 8 1 3 5 7 7 7 8 1 1 2 2 2 2 6 6 1 6 6 6 6 4 2 6 3 1 4 9 9 0 3 4 7 4 6 9 9 9 9
Carcass ID Number	2 3 3 2 3 2 3 3 3 2 3 2 2 3 2 2 3 3 3 3 2 2 2 2 2 5 3 1 7 1 5 2 6 1 7 6 9 8 6 6 7 0 0 1 2 8 6 6 8 9 1 1 1 1 2 2 1 1 3 3 4 5 4 5 2 5 2 3 5 5 5 3 4 2 3
Genital System	
Coagulating gland	
Epididymis	+ +
Penis	+ + + + + + + +
Preputial gland	+ + + +
Prostate	+ + + + M +
Seminal vesicle	+
Testes	+ +
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ M + + + + I + M M + + + + + + + + + + + + + + + +
Mediastinal, fibrosarcoma, metastatic, skin	X
Lymph node, mesenteric	+ M + + + + I + M M + + + + + + + + + + + + + + + +
Spleen	+ M + + + + + + + M + + + + + + + + + + + + + + +
Thymus	+ M + M + + + M I M M M M M + M M + + M M + + I +
Integumentary System	
Mammary gland	+ M M M M M M M M M M M M M M M M M M M M M M M M M
Skin	+ +
Fibrosarcoma	X X X X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Thoracic, fibrosarcoma, metastatic, skin	X
Nervous System	
Brain	+ M +
Spinal cord	+ +
Respiratory System	
Lung	+ M +
Alveolar/bronchiolar adenoma	X
Fibrosarcoma, metastatic, skin	X X
Hepatocellular carcinoma, metastatic, liver	
Nose	+ M +
Trachea	+ M +
Fibrosarcoma, metastatic, skin	X X
Special Senses System	
Eye	+
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ M +
Ureter	+
Urinary bladder	+ + + + A + + + + + + + + + + A + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant mixed	X X X

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	000	000	000	000	000	000	000	000	000	000	000	000	011	011	011
Carcass ID Number	294	301	404	233	355	411	522	553	636	533	544	555	572	581	591	505	514	532	543	542	544	562	621	655	674
Genital System																									
Coagulating gland									+																
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+															
Preputial gland																	+								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Mediastinal, fibrosarcoma, metastatic, skin																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	I	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	+	M	+	M	+	M	+	M	M	M	M	M	M	M	+	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Thoracic, fibrosarcoma, metastatic, skin																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X	X			X	X													X			X	X	
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Special Senses System																									
Eye		+											+												
Harderian gland													+												
Adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed					X					X							X								

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	2 8 3	2 9 2	3 2 2	3 2 3	3 3 3	3 4 3	4 4 5	3 5 1	5 5 4	3 5 5	**Total Tissues/ Tumors**
Genital System											
Coagulating gland											1
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis			+								8
Preputial gland			+					+			6
Prostate	+	+	+	+	+	+	+	+	+	+	59
Seminal vesicle										+	2
Testes	+	+	+	+	+	+	+	+	+	+	60
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	55
Mediastinal, fibrosarcoma, metastatic, skin											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	55
Spleen	+	+	+	+	+	+	+	+	+	+	58
Thymus	+	+	+	+	+	I	+	+	M	+	42
Integumentary System											
Mammary gland	+	M	M	M	M	M	M	M	+	M	9
Skin	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma											4
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Thoracic, fibrosarcoma, metastatic, skin											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	58
Spinal cord											2
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	59
Alveolar/bronchiolar adenoma	X								X		10
Fibrosarcoma, metastatic, skin											2
Hepatocellular carcinoma, metastatic, liver											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	59
Fibrosarcoma, metastatic, skin											2
Special Senses System											
Eye											3
Harderian gland			+								3
Adenoma			X								3
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Ureter											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	58
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed					X						7

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg

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

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

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

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	5 4 4	5 6 3	5 7 3	6 0 4	5 0 1	5 1 2	5 3 3	5 5 3	5 6 4	5 9 3	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	M	+	+	+	+	+	+	+	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	57
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	56
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	39
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	37
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma										X	1
Hepatocellular carcinoma		X		X							5
Hepatocellular adenoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	57
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	54
Tooth											2
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	59
Heart	+	+	+	+	+	+	+	+	+	+	60
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Subcapsular, adenoma		X									2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	58
Parathyroid gland	+	+	+	M	+	M	+	+	M	+	35
Pituitary gland	I	+	+	+	+	+	+	+	+	+	56
Thyroid gland	+	+	+	+	+	+	+	+	+	+	57
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis											1
Preputial gland											8
Prostate	+	+	+	+	+	+	+	+	+	+	57
Seminal vesicle											5
Testes	+	+	+	+	+	+	+	+	+	+	60

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	0 0 0 0 0 1 1 1 1 2 3 3 4 4 4 4 4 4 4 4 4 5 5 0 1 5 6 6 0 3 4 9 6 2 6 2 2 3 3 4 4 4 6 6 9 9 0 2 4 8 9 2 3 4 5 9 0 8 4 7 4 8 1 4 3 7 7 7 8 5 7 4 8
Carcass ID Number	5 6 4 5 5 4 5 5 5 4 5 5 5 5 5 4 5 5 6 5 5 5 5 5 5 8 0 9 3 9 9 2 8 7 9 2 4 8 8 2 9 2 0 0 3 4 9 5 2 1 1 1 1 1 1 2 1 2 1 3 2 1 4 3 5 4 4 3 2 5 2 5 5 3 1
Hematopoietic System	
Bone marrow	+ +
Lymph node	A A + + + + M + + + + + + + + M + + M + M + + M +
Lymph node, mesenteric	A A + + + + M A + + + + + + + M + + M + M + + M +
Spleen	+ +
Thymus	+ + + M + + + + M + + + + M + M + + M M M M M + M
Integumentary System	
Mammary gland	M M M M M M M M M M M M M M M M M M M M M M M M M
Skin	+ + + + I +
Fibrosarcoma	X
Neurofibrosarcoma	
Sarcoma	
Musculoskeletal System	
Bone	+ +
Skeletal muscle	
Fibrosarcoma, metastatic	
Nervous System	
Brain	+ +
Spinal cord	+ + + +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Alveolar/bronchiolar adenoma, multiple	
Fibrosarcoma, metastatic, skin	
Nose	+ +
Trachea	+ +
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ +
Urinary bladder	A + + + + + I + + + + + + A + + + + + + + + A + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant mixed	

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	5 4 1	5 4 5	5 5 3	5 8 1	5 8 8	5 9 4	5 9 9	6 2 3	6 4 5	6 6 9	6 7 9	6 9 5	7 1 1	7 2 6	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
Carcass ID Number	5 6 2	5 7 5	5 6 5	5 5 4	5 4 5	6 0 3	5 0 5	5 1 3	5 9 4	5 3 2	5 0 2	5 5 1	5 7 2	5 8 5	5 0 4	5 1 4	5 4 3	5 5 2	5 6 1	5 7 4	5 9 2	6 0 5	4 9 5	5 1 5	5 3 4
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	M	M	M	M	M	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X	X															
Neurofibrosarcoma							X																	
Sarcoma				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																	
Fibrosarcoma, metastatic							X																	
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																								
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X															X	X		
Alveolar/bronchiolar adenoma, multiple													X											
Fibrosarcoma, metastatic, skin								X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X		X											

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	5 4 4	5 6 3	5 7 3	6 0 4	5 0 1	5 1 2	5 3 3	5 5 3	5 6 4	5 9 3	**Total Tissues/ Tumors**
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	60
Thymus	+	+	+	+	+	+	+	+	+	M	38
Integumentary System											
Mammary gland	+	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	59
Fibrosarcoma											3
Neurofibrosarcoma	X										2
Sarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Fibrosarcoma, metastatic											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Spinal cord											4
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma							X				4
Alveolar/bronchiolar adenoma, multiple											1
Fibrosarcoma, metastatic, skin											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Harderian gland					+						2
Adenoma					X						2
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Urinary bladder	+	+	+	+	+	+	+	+	+	+	54
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed		X		X				X			5

TABLE C3
Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Harderian Gland: Adenoma			
Overall rates[a]	2/60 (3%)	3/60 (5%)	2/60 (3%)
Adjusted rates[b]	4.3%	7.2%	7.1%
Terminal rates[c]	2/46 (4%)	2/39 (5%)	1/21 (5%)
First incidence (days)	729 (T)	670	467
Life table tests[d]	P=0.312	P=0.433	P=0.442
Logistic regression tests[d]	P=0.458	P=0.451	P=0.609
Cochran-Armitage test[d]	P=0.593		
Fisher exact test[d]		P=0.500	P=0.691N
Liver: Hepatocellular Adenoma			
Overall rates	6/60 (10%)	6/59 (10%)	1/59 (2%)
Adjusted rates	12.7%	14.8%	4.2%
Terminal rates	5/46 (11%)	5/39 (13%)	0/21 (0%)
First incidence (days)	702	673	695
Life table tests	P=0.285N	P=0.505	P=0.274N
Logistic regression tests	P=0.224N	P=0.535	P=0.220N
Cochran-Armitage test	P=0.059N		
Fisher exact test		P=0.607	P=0.060N
Liver: Hepatocellular Carcinoma			
Overall rates	6/60 (10%)	2/59 (3%)	5/59 (8%)
Adjusted rates	11.7%	4.7%	19.9%
Terminal rates	3/46 (7%)	1/39 (3%)	3/21 (14%)
First incidence (days)	517	670	581
Life table tests	P=0.322	P=0.188N	P=0.292
Logistic regression tests	P=0.550	P=0.146N	P=0.553
Cochran-Armitage test	P=0.440N		
Fisher exact test		P=0.142N	P=0.512N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	12/60 (20%)	8/59 (14%)	6/59 (10%)
Adjusted rates	23.6%	19.1%	23.3%
Terminal rates	8/46 (17%)	6/39 (15%)	3/21 (14%)
First incidence (days)	517	670	581
Life table tests	P=0.528N	P=0.359N	P=0.581
Logistic regression tests	P=0.282N	P=0.295N	P=0.346N
Cochran-Armitage test	P=0.082N		
Fisher exact test		P=0.244N	P=0.107N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	9/60 (15%)	10/59 (17%)	5/60 (8%)
Adjusted rates	19.6%	25.6%	20.7%
Terminal rates	9/46 (20%)	10/39 (26%)	3/21 (14%)
First incidence (days)	729 (T)	729 (T)	594
Life table tests	P=0.373	P=0.342	P=0.487
Logistic regression tests	P=0.462	P=0.342	P=0.602
Cochran-Armitage test	P=0.174N		
Fisher exact test		P=0.484	P=0.197N

TABLE C3
Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	4/60 (7%)	0/59 (0%)	0/60 (0%)
Adjusted rates	8.7%	0.0%	0.0%
Terminal rates	4/46 (9%)	0/39 (0%)	0/21 (0%)
First incidence (days)	729 (T)	–[e]	–
Life table tests	P=0.044N	P=0.086N	P=0.203N
Logistic regression tests	P=0.044N	P=0.086N	P=0.203N
Cochran-Armitage test	P=0.015N		
Fisher exact test		P=0.061N	P=0.059N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	12/60 (20%)	10/59 (17%)	5/60 (8%)
Adjusted rates	26.1%	25.6%	20.7%
Terminal rates	12/46 (26%)	10/39 (26%)	3/21 (14%)
First incidence (days)	729 (T)	729 (T)	594
Life table tests	P=0.477N	P=0.579N	P=0.526N
Logistic regression tests	P=0.387N	P=0.579N	P=0.410N
Cochran-Armitage test	P=0.049N		
Fisher exact test		P=0.424N	P=0.057N
Skin: Fibrosarcoma			
Overall rates	1/60 (2%)	4/60 (7%)	3/60 (5%)
Adjusted rates	2.2%	8.8%	9.5%
Terminal rates	1/46 (2%)	0/39 (0%)	0/21 (0%)
First incidence (days)	729 (T)	581	495
Life table tests	P=0.080	P=0.147	P=0.127
Logistic regression tests	P=0.205	P=0.170	P=0.267
Cochran-Armitage test	P=0.253		
Fisher exact test		P=0.182	P=0.309
All Organs: Hemangioma			
Overall rates	3/60 (5%)	1/60 (2%)	0/60 (0%)
Adjusted rates	6.5%	2.1%	0.0%
Terminal rates	3/46 (7%)	0/39 (0%)	0/21 (0%)
First incidence (days)	729 (T)	639	–
Life table tests	P=0.146N	P=0.361N	P=0.289N
Logistic regression tests	P=0.106N	P=0.337N	P=0.289N
Cochran-Armitage test	P=0.061N		
Fisher exact test		P=0.309N	P=0.122N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	4/60 (7%)	2/60 (3%)	1/60 (2%)
Adjusted rates	8.7%	4.6%	4.8%
Terminal rates	4/46 (9%)	1/39 (3%)	1/21 (5%)
First incidence (days)	729 (T)	639	729 (T)
Life table tests	P=0.326N	P=0.411N	P=0.473N
Logistic regression tests	P=0.265N	P=0.384N	P=0.473N
Cochran-Armitage test	P=0.119N		
Fisher exact test		P=0.340N	P=0.182N

TABLE C3
Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Malignant Lymphoma (Mixed)			
Overall rates	8/60 (13%)	7/60 (12%)	5/60 (8%)
Adjusted rates	16.1%	16.0%	21.3%
Terminal rates	5/46 (11%)	4/39 (10%)	3/21 (14%)
First incidence (days)	637	573	679
Life table tests	P=0.388	P=0.598	P=0.420
Logistic regression tests	P=0.537N	P=0.560N	P=0.581
Cochran-Armitage test	P=0.234N		
Fisher exact test		P=0.500N	P=0.279N
All Organs: Benign Tumors			
Overall rates	20/60 (33%)	21/60 (35%)	11/60 (18%)
Adjusted rates	42.5%	49.6%	40.7%
Terminal rates	19/46 (41%)	18/39 (46%)	6/21 (29%)
First incidence (days)	702	639	467
Life table tests	P=0.298	P=0.256	P=0.399
Logistic regression tests	P=0.534	P=0.302	P=0.539N
Cochran-Armitage test	P=0.043N		
Fisher exact test		P=0.500	P=0.047N
All Organs: Malignant Tumors			
Overall rates	21/60 (35%)	14/60 (23%)	13/60 (22%)
Adjusted rates	39.3%	29.3%	44.5%
Terminal rates	14/46 (30%)	6/39 (15%)	6/21 (29%)
First incidence (days)	517	573	495
Life table tests	P=0.352	P=0.261N	P=0.296
Logistic regression tests	P=0.289N	P=0.160N	P=0.426N
Cochran-Armitage test	P=0.061N		
Fisher exact test		P=0.114N	P=0.078N
All Organs: Benign and Malignant Tumors			
Overall rates	32/60 (53%)	32/60 (53%)	21/60 (35%)
Adjusted rates	60.2%	65.2%	66.6%
Terminal rates	25/46 (54%)	22/39 (56%)	11/21 (52%)
First incidence (days)	517	573	467
Life table tests	P=0.096	P=0.269	P=0.121
Logistic regression tests	P=0.519N	P=0.367	P=0.552N
Cochran-Armitage test	P=0.027N		
Fisher exact test		P=0.573N	P=0.033N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group

TABLE C4
Historical Incidence of Integumentary Sarcomas in Male B6C3F$_1$ Mice Receiving Water Vehicle by Gavage

	Incidence in Controls			
	Fibrosarcoma	Neurofibrosarcoma	Sarcoma	Fibrosarcoma or Neurofibrosarcoma
Overall Historical Incidence[a]				
Total	74/555 (13.3%)	1/555 (0.2%)	13/555 (2.3%)	75/555 (13.5%)
Standard deviation	7.4%	0.6%	2.8%	7.6%
Range	4%-30%	0%-2%	0%-8%	4%-30%

[a] Data as of 22 December 1989 for 2-year studies on the Toxicology Data Management System, and as of 6 March 1990 for 2-year studies on the Carcinogenesis Bioassay Data System. Subcutaneous sarcomas only are included for data derived from the Toxicology Data Management System; integumentary sarcomas occurring at all sites are included for data derived from the Carcinogenesis Bioassay Data System. No historical control data were available for water gavage studies conducted at the International Research and Development Corporation.

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	7	11	26
Moribund	5	10	8
Accidental deaths	2	0	5
Survivors			
Terminal sacrifice	46	39	21
Animals examined microscopically	60	60	60
Alimentary System			
Esophagus	(59)	(60)	(60)
Ulcer, acute		1 (2%)	
Gallbladder	(51)	(52)	(39)
Cyst		1 (2%)	
Inflammation, chronic		1 (2%)	
Intestine large, cecum	(55)	(55)	(44)
Diverticulum			1 (2%)
Parasite metazoan			2 (5%)
Intestine large, colon	(59)	(58)	(56)
Infiltration cellular, plasma cell		1 (2%)	
Inflammation, chronic active			1 (2%)
Parasite metazoan	5 (8%)	4 (7%)	9 (16%)
Intestine large, rectum	(58)	(58)	(50)
Inflammation, acute		1 (2%)	
Parasite metazoan			1 (2%)
Intestine small, ileum	(54)	(54)	(37)
Amyloid deposition		1 (2%)	
Parasite metazoan		1 (2%)	
Intestine small, jejunum	(53)	(56)	(40)
Hyperplasia, lymphoid	1 (2%)		
Liver	(60)	(59)	(59)
Basophilic focus			1 (2%)
Basophilic focus, multiple	1 (2%)		
Clear cell focus			1 (2%)
Congestion		1 (2%)	1 (2%)
Cytoplasmic alteration		1 (2%)	
Hematopoietic cell proliferation			1 (2%)
Infarct		2 (3%)	
Inflammation, acute	1 (2%)		2 (3%)
Inflammation, chronic	3 (5%)	4 (7%)	2 (3%)
Inflammation, chronic active, multifocal	1 (2%)		
Necrosis	2 (3%)	4 (7%)	5 (8%)
Bile duct, cyst	1 (2%)		1 (2%)
Centrilobular, fatty change			1 (2%)
Hepatocyte, cytomegaly, diffuse			1 (2%)
Hepatocyte, necrosis	1 (2%)		
Mesentery	(4)	(1)	
Inflammation, chronic	2 (50%)		
Artery, perivascular, inflammation, chronic		1 (100%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Pancreas	(58)	(59)	(57)
Atrophy	3 (5%)	1 (2%)	4 (7%)
Cyst		1 (2%)	
Hyperplasia, focal	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Necrosis, multifocal	1 (2%)		
Duct, cyst	1 (2%)		
Salivary glands	(60)	(57)	(60)
Atrophy		2 (4%)	
Stomach, forestomach	(60)	(60)	(59)
Cyst		1 (2%)	1 (2%)
Diverticulum	3 (5%)		
Erosion	1 (2%)		
Hyperkeratosis	1 (2%)		
Hyperplasia, squamous, focal	5 (8%)	2 (3%)	8 (14%)
Hyperplasia, squamous, multifocal			5 (8%)
Inflammation, acute	1 (2%)		
Inflammation, acute, multifocal			1 (2%)
Inflammation, chronic active			1 (2%)
Ulcer		2 (3%)	1 (2%)
Stomach, glandular	(58)	(59)	(54)
Cyst		3 (5%)	1 (2%)
Erosion	1 (2%)	3 (5%)	8 (15%)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Epithelium, hyperplasia, focal	1 (2%)		
Tooth	(5)	(2)	(2)
Developmental malformation		1 (50%)	
Peridontal tissue, inflammation, acute	1 (20%)	1 (50%)	
Peridontal tissue, inflammation, chronic			1 (50%)
Pulp, inflammation, acute	3 (60%)		1 (50%)
Cardiovascular System			
Heart	(60)	(59)	(60)
Abscess, chronic active			1 (2%)
Degeneration	21 (35%)	16 (27%)	19 (32%)
Inflammation, acute, multifocal	1 (2%)		
Inflammation, chronic		3 (5%)	
Mineralization	1 (2%)		3 (5%)
Atrium, pigmentation		1 (2%)	
Atrium, thrombus		1 (2%)	1 (2%)
Epicardium, fibrosis		1 (2%)	
Epicardium, inflammation, chronic	1 (2%)		
Valve, pigmentation	8 (13%)	10 (17%)	
Ventricle, thrombus	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System			
Adrenal gland, cortex	(60)	(59)	(60)
Basophilic focus			1 (2%)
Cyst	1 (2%)		
Cytoplasmic alteration, focal	1 (2%)		1 (2%)
Hyperplasia	4 (7%)	1 (2%)	3 (5%)
Hyperplasia, focal	1 (2%)		
Hypertrophy, focal	1 (2%)		1 (2%)
Subcapsular, hyperplasia	54 (90%)	48 (81%)	49 (82%)
Adrenal gland, medulla	(59)	(59)	(60)
Fibrosis			2 (3%)
Hyperplasia	1 (2%)		
Hyperplasia, focal			1 (2%)
Islets, pancreatic	(56)	(59)	(58)
Hyperplasia	1 (2%)		
Parathyroid gland	(41)	(19)	(35)
Cyst	1 (2%)	2 (11%)	1 (3%)
Pituitary gland	(56)	(57)	(56)
Congestion			1 (2%)
Cyst	2 (4%)		2 (4%)
Hyperplasia, focal	1 (2%)		
Thyroid gland	(60)	(58)	(57)
Inflammation, chronic	2 (3%)		
Mineralization	1 (2%)		
Follicle, cyst	6 (10%)	3 (5%)	2 (4%)
Follicular cell, hyperplasia	1 (2%)	2 (3%)	1 (2%)
General Body System			
None			
Genital System			
Coagulating gland		(1)	
Cyst		1 (100%)	
Epididymis	(60)	(60)	(60)
Dilatation		1 (2%)	
Inflammation, chronic	1 (2%)		
Preputial gland	(8)	(6)	(8)
Abscess	2 (25%)		
Fibrosis			1 (13%)
Hemorrhage		1 (17%)	
Inflammation, acute	1 (13%)		
Inflammation, chronic	1 (13%)	2 (33%)	1 (13%)
Inflammation, granulomatous	3 (38%)		
Duct, cyst	5 (63%)	4 (67%)	4 (50%)
Prostate	(59)	(59)	(57)
Fibrosis		1 (2%)	
Fibrosis, focal			1 (2%)
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Genital System (continued)			
Seminal vesicle	(5)	(2)	(5)
Dilatation	1 (20%)	1 (50%)	1 (20%)
Testes	(60)	(60)	(60)
Degeneration	3 (5%)	4 (7%)	4 (7%)
Infiltration cellular, lymphocytic, focal			1 (2%)
Mineralization	2 (3%)	8 (13%)	2 (3%)
Unilateral, atrophy	2 (3%)		
Hematopoietic System			
Bone marrow	(60)	(60)	(60)
Myeloid cell, hyperplasia	3 (5%)	4 (7%)	
Lymph node	(58)	(55)	(51)
Iliac, hyperplasia, plasma cell			1 (2%)
Inguinal, hyperplasia, lymphoid	2 (3%)		
Inguinal, hyperplasia, plasma cell	4 (7%)	2 (4%)	1 (2%)
Inguinal, inflammation, acute	1 (2%)		
Inguinal, pigmentation	2 (3%)	9 (16%)	
Mediastinal, hemorrhage	1 (2%)		
Pancreatic, hyperplasia, lymphoid	1 (2%)		
Lymph node, mesenteric	(56)	(55)	(50)
Congestion, focal			1 (2%)
Hematopoietic cell proliferation granulocytic	1 (2%)		
Hematopoietic cell proliferation erythrocytic			1 (2%)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Hyperplasia, plasma cell			1 (2%)
Infiltration cellular, histiocytic			1 (2%)
Inflammation, acute	1 (2%)	2 (4%)	
Pigmentation, hemosiderin			1 (2%)
Spleen	(59)	(58)	(60)
Atrophy, focal		1 (2%)	
Cyst			1 (2%)
Hematopoietic cell proliferation granulocytic	4 (7%)	3 (5%)	
Hematopoietic cell proliferation erythrocytic	1 (2%)	1 (2%)	6 (10%)
Hyperplasia, lymphoid	1 (2%)	2 (3%)	5 (8%)
Hyperplasia, plasma cell	1 (2%)		3 (5%)
Infarct	1 (2%)		
Infiltration cellular, histiocytic			1 (2%)
Pigmentation, hemosiderin			2 (3%)
Capsule, fibrosis		1 (2%)	1 (2%)
Thymus	(49)	(42)	(38)
Atrophy	4 (8%)	1 (2%)	1 (3%)
Cyst	4 (8%)	3 (7%)	4 (11%)
Ectopic parathyroid gland	1 (2%)	3 (7%)	
Necrosis		1 (2%)	1 (3%)
Epithelial cell, hyperplasia	9 (18%)	7 (17%)	8 (21%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System			
Mammary gland	(13)	(9)	(3)
Hemorrhage, focal	1 (8%)		
Skin	(60)	(60)	(59)
Abscess	1 (2%)		
Acanthosis	1 (2%)		2 (3%)
Fibrosis	1 (2%)	2 (3%)	2 (3%)
Hyperkeratosis	1 (2%)		
Hyperplasia, basal cell, focal	1 (2%)		
Inflammation, acute		1 (2%)	2 (3%)
Inflammation, chronic		1 (2%)	2 (3%)
Parasite external	2 (3%)	3 (5%)	7 (12%)
Ulcer	1 (2%)		4 (7%)
Epithelium, atrophy			1 (2%)
Hair follicle, atrophy			2 (3%)
Prepuce, abscess		1 (2%)	
Prepuce, inflammation, acute	1 (2%)		2 (3%)
Prepuce, ulcer			3 (5%)
Scrotal, ulcer, acute			1 (2%)
Subcutaneous tissue, inflammation, chronic	1 (2%)		
Musculoskeletal System			
Bone	(60)	(60)	(60)
Fracture healed	1 (2%)		1 (2%)
Osteoporosis, focal	1 (2%)		
Skeletal muscle	(1)	(1)	(1)
Inflammation, chronic	1 (100%)		
Nervous System			
Brain	(60)	(58)	(60)
Congestion		1 (2%)	
Inflammation, acute, multifocal	1 (2%)		
Melanosis		1 (2%)	
Mineralization	45 (75%)	34 (59%)	28 (47%)
Necrosis, focal	1 (2%)		
Meninges, perivascular, inflammation, chronic	1 (2%)		
Respiratory System			
Lung	(60)	(59)	(60)
Congestion	1 (2%)	2 (3%)	11 (18%)
Hemorrhage	1 (2%)		2 (3%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	4 (7%)	2 (3%)
Alveolus, infiltration cellular, histiocytic	2 (3%)	3 (5%)	3 (5%)
Interstitium, inflammation, chronic		2 (3%)	2 (3%)
Perivascular, infiltration cellular, lymphocytic	5 (8%)	6 (10%)	2 (3%)
Pleura, fibrosis		1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Respiratory System (continued)			
Nose	(60)	(59)	(60)
Exudate	15 (25%)	18 (31%)	22 (37%)
Granuloma	2 (3%)	1 (2%)	
Inflammation, acute	3 (5%)	7 (12%)	24 (40%)
Inflammation, chronic	2 (3%)	2 (3%)	
Inflammation, chronic active		2 (3%)	
Mucosa, turbinate, hyperplasia			1 (2%)
Mucosa, nasolacrimal duct, hyperplasia	23 (38%)	28 (47%)	24 (40%)
Nasolacrimal duct, inflammation, acute	1 (2%)	2 (3%)	3 (5%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)		
Olfactory epithelium, metaplasia		3 (5%)	2 (3%)
Submucosa, cyst	1 (2%)		
Turbinate, atrophy			1 (2%)
Turbinate, inflammation, chronic, multifocal	1 (2%)		
Vomeronasal organ, cyst	1 (2%)		
Trachea	(60)	(59)	(60)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic active			1 (2%)
Metaplasia, squamous		1 (2%)	
Ulcer, acute		1 (2%)	
Special Senses System			
Eye		(3)	
Inflammation, acute		1 (33%)	
Neovascularization		2 (67%)	
Cornea, necrosis		1 (33%)	
Harderian gland	(3)	(3)	(2)
Cyst, multiple	1 (33%)		
Inflammation, chronic	1 (33%)		
Urinary System			
Kidney	(60)	(59)	(60)
Cyst	3 (5%)	4 (7%)	5 (8%)
Inflammation, acute	1 (2%)		2 (3%)
Mineralization	2 (3%)	2 (3%)	2 (3%)
Nephropathy	36 (60%)	38 (64%)	28 (47%)
Capsule, fibrosis			1 (2%)
Pelvis, inflammation, chronic	2 (3%)		
Renal tubule, hyperplasia, focal	1 (2%)		
Renal tubule, necrosis, acute			6 (10%)
Urinary bladder	(57)	(58)	(54)
Calculus gross observation	1 (2%)		
Diverticulum	1 (2%)		
Ectopic tissue			1 (2%)
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		
Transitional epithelium, hyperplasia, focal			1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF MONOCHLOROACETIC ACID

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	9	12	9
Moribund	8	8	4
Accidental deaths	1	0	3
Survivors			
Terminal sacrifice	41	40	44
Dead	1	0	0
Animals examined microscopically	60	60	60
Alimentary System			
Esophagus	(60)		(60)
Gallbladder	(55)	(1)	(51)
Histiocytic sarcoma			1 (2%)
Intestine large, cecum	(52)		(53)
Histiocytic sarcoma			1 (2%)
Intestine large, rectum	(60)		(58)
Histiocytic sarcoma	1 (2%)		
Intestine small, ileum	(52)		(54)
Histiocytic sarcoma			1 (2%)
Intestine small, jejunum	(52)	(1)	(54)
Histiocytic sarcoma			1 (2%)
Liver	(60)	(60)	(60)
Granulosa cell tumor malignant, metastatic, ovary		1 (2%)	
Hemangiosarcoma	1 (2%)		
Hepatocellular carcinoma		1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)	2 (3%)
Histiocytic sarcoma	3 (5%)	2 (3%)	1 (2%)
Mesentery	(23)	(7)	(16)
Histiocytic sarcoma	2 (9%)	1 (14%)	1 (6%)
Sarcoma, metastatic, uterus			1 (6%)
Pancreas	(60)		(60)
Histiocytic sarcoma			1 (2%)
Sarcoma, metastatic, uterus			1 (2%)
Salivary glands	(59)		(60)
Histiocytic sarcoma			1 (2%)
Stomach, forestomach	(60)	(59)	(60)
Papilloma squamous			2 (3%)
Stomach, glandular	(57)	(60)	(60)
Histiocytic sarcoma		1 (2%)	1 (2%)
Cardiovascular System			
Heart	(60)	(60)	(60)
Fibrosarcoma, metastatic, skin		1 (2%)	
Histiocytic sarcoma	2 (3%)	1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System			
Adrenal gland, cortex	(59)	(1)	(60)
Histiocytic sarcoma			1 (2%)
Subcapsular, adenoma	1 (2%)		
Adrenal gland, medulla	(57)		(59)
Pheochromocytoma malignant	1 (2%)		
Pheochromocytoma benign			1 (2%)
Islets, pancreatic	(59)		(59)
Adenoma	1 (2%)		
Parathyroid gland	(34)		(43)
Pituitary gland	(55)	(6)	(57)
Adenoma	5 (9%)	6 (100%)	7 (12%)
Pars intermedia, adenoma	1 (2%)		1 (2%)
Thyroid gland	(60)	(1)	(60)
Histiocytic sarcoma			1 (2%)
Follicular cell, adenoma	1 (2%)	1 (100%)	2 (3%)
General Body System			
None			
Genital System			
Ovary	(59)	(24)	(60)
Adenocarcinoma, metastatic, uterus			1 (2%)
Adenoma, papillary	1 (2%)		
Choriocarcinoma		1 (4%)	
Cystadenoma	1 (2%)		
Granulosa cell tumor malignant		1 (4%)	
Granulosa cell tumor benign	1 (2%)	1 (4%)	
Histiocytic sarcoma	2 (3%)	1 (4%)	
Mixed tumor benign	1 (2%)		
Oviduct	(1)		
Uterus	(60)	(43)	(60)
Adenocarcinoma			2 (3%)
Hemangioma			1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	
Leiomyosarcoma			1 (2%)
Sarcoma			1 (2%)
Endometrium, deciduoma benign	1 (2%)		
Endometrium, histiocytic sarcoma			1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System			
Bone marrow	(60)	(21)	(60)
Plasma cell tumor NOS			1 (2%)
Lymph node	(60)	(19)	(58)
Axillary, sarcoma, metastatic		1 (5%)	
Bronchial, histiocytic sarcoma	1 (2%)		
Iliac, histiocytic sarcoma	1 (2%)	1 (5%)	1 (2%)
Inguinal, histiocytic sarcoma			1 (2%)
Mediastinal, fibrosarcoma, metastatic, skin		1 (5%)	
Mediastinal, histiocytic sarcoma			1 (2%)
Pancreatic, histiocytic sarcoma		1 (5%)	
Renal, histiocytic sarcoma		1 (5%)	1 (2%)
Lymph node, mesenteric	(60)	(12)	(58)
Histiocytic sarcoma	2 (3%)	1 (8%)	1 (2%)
Sarcoma, metastatic, uterus			1 (2%)
Spleen	(60)	(25)	(60)
Histiocytic sarcoma	1 (2%)	1 (4%)	2 (3%)
Thymus	(54)	(3)	(53)
Integumentary System			
Mammary gland	(59)	(4)	(60)
Adenocarcinoma	2 (3%)	2 (50%)	1 (2%)
Adenocarcinoma, multiple			1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)
Skin	(60)	(50)	(60)
Fibrosarcoma	2 (3%)	2 (4%)	1 (2%)
Sarcoma		1 (2%)	
Musculoskeletal System			
Bone	(60)	(1)	(60)
Skeletal muscle	(3)	(2)	(2)
Adenocarcinoma, metastatic, uterus			1 (50%)
Fibrosarcoma, metastatic, skin	1 (33%)		
Sarcoma	1 (33%)		
Nervous System			
Brain	(60)	(1)	(60)
Respiratory System			
Lung	(60)	(14)	(60)
Alveolar/bronchiolar adenoma		2 (14%)	2 (3%)
Alveolar/bronchiolar carcinoma		1 (7%)	
Fibrosarcoma, metastatic, skin	1 (2%)	1 (7%)	
Histiocytic sarcoma		1 (7%)	1 (2%)
Nose	(60)	(60)	(60)
Trachea	(60)		(60)
Histiocytic sarcoma			1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Special Senses System			
Eye		(1)	(1)
Harderian gland	(1)		
Adenoma	1 (100%)		
Urinary System			
Kidney	(60)	(5)	(60)
Adenocarcinoma, metastatic, uterus			1 (2%)
Histiocytic sarcoma		1 (20%)	2 (3%)
Ureter	(1)	(1)	
Urinary bladder	(57)	(1)	(56)
Histiocytic sarcoma	1 (2%)		1 (2%)
Sarcoma, metastatic, uterus			1 (2%)
Systemic Lesions			
Multiple organs[a]	(60)	(60)	(60)
Histiocytic sarcoma	3 (5%)	2 (3%)	3 (5%)
Lymphoma malignant lymphocytic	2 (3%)	3 (5%)	
Lymphoma malignant mixed	27 (45%)	14 (23%)	13 (22%)
Lymphoma malignant undifferentiated cell		1 (2%)	
Tumor Summary			
Total animals with primary neoplasms[b]	41	33	27
Total primary neoplasms	55	40	42
Total animals with benign neoplasms	14	11	13
Total benign neoplasms	16	11	18
Total animals with malignant neoplasms	36	27	20
Total malignant neoplasms	39	29	23
Total animals with secondary neoplasms[c]	1	3	2
Total secondary neoplasms	3	5	7
Total animals with neoplasms uncertain-benign or malignant			1
Total uncertain neoplasms			1

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control

Number of Days on Study	1 5 3	4 6 3	5 1 1	5 1 3	6 2 5	6 2 7	6 3 6	6 5 7	6 7 1	6 7 9	6 8 2	6 8 3	6 8 7	7 0 8	7 0 9	7 1 7	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 1 6 1	1 5 1	1 1 8 1	1 7 1	2 3 4	2 1 5	2 2 4	2 2 3	1 7 2	1 7 4	1 6 3	1 4 3	2 0 4	1 5 5	1 5 2	2 4 5	1 8 4	1 9 4	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 9 2	2 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	M	A	A	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Intestine small	+	+	+	+	A	+	A	A	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	A	A	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	A	A	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	A	A	+	+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Hepatocellular adenoma																								X	
Histiocytic sarcoma				X											X										
Mesentery		+		+	+				+	+		+	+	+					+					+	
Histiocytic sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tooth															+										
Cardiovascular System																									
Blood vessel	+	+	+	+	M	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X											X										
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																									

+: 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 Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731
Carcass ID Number	20223	21225	21424	22131	23335	23535	24144	31355	34145	36464	36553	37373	37755	38585	39353	39555	40551	41211	42222	42423	43233	43141	44144	45353	45454
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular adenoma																									
Histiocytic sarcoma					X																				
Mesentery		+			+		+		+			+			+				+		+	+			
Histiocytic sarcoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma											X														
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	1 6 2	1 8 2	1 8 3	1 9 1	2 0 3	2 1 3	2 2 5	2 3 1	2 3 2	2 4 1	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	55
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Intestine small	+	+	+	+	+	+	+	+	+	+	53
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Hepatocellular adenoma											1
Histiocytic sarcoma											3
Mesentery			+		+		+	+			23
Histiocytic sarcoma											2
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	57
Tooth									+		2
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+		+	57
Heart	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Subcapsular, adenoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	57
Pheochromocytoma malignant					X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	1 5 3	4 6 3	5 1 1	5 1 3	6 2 5	6 2 7	6 3 6	6 5 7	6 7 1	6 7 9	6 8 2	6 8 3	6 8 7	7 0 8	7 0 9	7 1 7	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 6 1	1 5 1	1 8 1	1 7 1	2 3 4	2 1 5	2 2 4	2 2 3	1 7 2	1 7 4	1 6 3	1 4 3	2 0 4	1 5 5	1 5 2	2 4 5	1 8 4	1 9 4	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 9 2	2 0 1
Endocrine System (continued)																									
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	M	M	M	+	+	+	M	M	+	+	M	+	+	+	M
Pituitary gland	+	+	+	I	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																		X				X			X
Pars intermedia, adenoma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, papillary																									
Cystadenoma																									X
Granulosa cell tumor benign																									
Histiocytic sarcoma				X											X										
Mixed tumor benign																									
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Endometrium, deciduoma benign																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, histiocytic sarcoma																									
Iliac, histiocytic sarcoma				X																					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	I	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma											X														
Fibrosarcoma, metastatic, skin																X									
Histiocytic sarcoma				X																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																X					X				

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731
Carcass ID Number	20224	21224	21441	22131	23335	23544	24445	13155	14555	16464	16555	17733	17755	18555	19353	19955	20551	21122	22242	22423	23131	24144	25333	25444	25554
Endocrine System (continued)																									
Parathyroid gland	M	M	+	M	M	+	M	+	+	+	M	+	+	+	M	+	+	M	M	M	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X											X						
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, papillary		X																							
Cystadenoma																									
Granulosa cell tumor benign																									
Histiocytic sarcoma																									
Mixed tumor benign																									
Oviduct		+																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endometrium, deciduoma benign																	X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, histiocytic sarcoma					X																				
Iliac, histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	1 6 2	1 8 2	1 8 3	1 9 1	2 0 3	2 1 3	2 2 5	2 3 1	2 3 2	2 4 1	**Total Tissues/ Tumors**
Endocrine System (continued)											
Parathyroid gland	M	+	M	+	M	+	+	M	M	+	34
Pituitary gland	+	+	+	+	+	+	+	+	M	+	55
Adenoma											5
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicular cell, adenoma								X			1
General Body System											
None											
Genital System											
Ovary	+	+	+	+	+	+	+	+	+	+	59
Adenoma, papillary											1
Cystadenoma											1
Granulosa cell tumor benign						X					1
Histiocytic sarcoma											2
Mixed tumor benign									X		1
Oviduct											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Endometrium, deciduoma benign											1
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Bronchial, histiocytic sarcoma											1
Iliac, histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Spleen	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Thymus	+	+	+	+	+	+	+	+	+	+	54
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma											2
Fibrosarcoma, metastatic, skin											1
Histiocytic sarcoma											1
Skin	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma											2

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	1 5 3	4 6 3	5 1 1	5 1 3	6 2 5	6 2 7	6 3 6	6 5 7	6 7 1	6 7 9	6 8 2	6 8 3	6 8 7	7 0 8	7 0 9	7 1 7	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 6 1	1 5 1	1 8 1	1 7 1	2 3 4	2 1 5	2 2 4	2 2 3	1 7 2	1 7 4	1 6 3	1 4 3	2 0 4	1 5 5	1 5 2	2 4 5	1 8 4	1 9 4	1 3 2	1 3 3	1 3 4	1 4 1	1 4 2	1 9 2	2 0 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+						+									
Fibrosarcoma, metastatic, skin																X									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter															+										
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X											X										
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed								X	X	X	X	X	X	X			X	X							X

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731
Carcass ID Number	20223	21224	21141	22135	23335	23744	24145	13455	14564	16455	16533	17735	17855	18553	19335	19955	20551	21122	22242	22443	23131	24144	25343	25454
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+										
Fibrosarcoma, metastatic, skin																										
Sarcoma																X										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear								+									+									
Harderian gland																										
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																					
Lymphoma malignant lymphocytic	X																									
Lymphoma malignant mixed		X				X					X				X				X	X	X				X	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: Vehicle Control (continued)

Number of Days on Study	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	
Carcass ID Number	1 6 2	1 8 2	1 8 3	1 9 1	2 0 3	2 1 3	2 2 5	2 3 1	2 3 2	2 4 1	**Total Tissues/ Tumors**
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											3
Fibrosarcoma, metastatic, skin											1
Sarcoma											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma, metastatic, skin											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Ear											2
Harderian gland				+							1
Adenoma				X							1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Ureter											1
Urinary bladder	+	+	+	M	+	+	+	+	+	+	57
Histiocytic sarcoma											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											3
Lymphoma malignant lymphocytic											2
Lymphoma malignant mixed		X	X	X	X	X	X	X	X	X	27

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg

Number of Days on Study	2 5 3	3 1 0	3 9 0	5 0 3	5 4 5	5 4 5	5 8 7	5 9 0	5 9 1	6 1 4	6 3 6	6 4 0	6 4 7	6 5 1	6 5 6	6 7 5	6 9 7	7 0 1	7 0 3	7 0 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 2 2	4 6 1	4 1 1	3 7 1	4 3 1	4 6 2	3 9 1	4 1 3	3 8 3	3 8 5	3 9 3	4 5 2	4 7 4	4 7 1	4 5 4	4 4 5	4 7 3	3 9 5	3 7 2	3 7 5	3 9 2	3 9 4	4 0 2	4 0 4	4 2 4
Alimentary System																									
Gallbladder					A																				
Intestine small																								+	
Intestine small, jejunum																								+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary														X											
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Histiocytic sarcoma								X												X					
Mesentery				+																+	+				
Histiocytic sarcoma																				X					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																				X					
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin					X																				
Histiocytic sarcoma																				X					
Endocrine System																									
Adrenal gland				+																					
Adrenal gland, cortex				+																					
Pituitary gland																+									
Adenoma																X									
Thyroid gland																								+	
Follicular cell, adenoma																								X	
General Body System																									
None																									
Genital System																									
Ovary	+	+		+								+		+		+				+		+			
Choriocarcinoma	X																								
Granulosa cell tumor malignant														X											
Granulosa cell tumor benign																									
Histiocytic sarcoma																				X					
Uterus		+									+	+	+		+	+	+			+	+	+		+	+
Histiocytic sarcoma																				X					
Hematopoietic System																									
Bone marrow													+							+	+		+		+
Lymph node			+	+	+	+	+		+	+	+			+		+		+		+					+
Axillary, sarcoma, metastatic							X																		
Iliac, histiocytic sarcoma																				X					
Mediastinal, fibrosarcoma, metastatic, skin					X																				

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	43 3	43 5	44 3	45 1	46 5	47 3	47 5	48 1	48 4	37 4	38 1	38 2	38 4	40 5	41 5	42 3	42 5	43 4	44 2	45 3	46 4	48 3	40 1	40 3	41 2
Alimentary System																									
Gallbladder																									
Intestine small																									
Intestine small, jejunum																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary																									
Hepatocellular carcinoma	X																								
Hepatocellular adenoma								X																	
Histiocytic sarcoma																									
Mesentery	+						+																		
Histiocytic sarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																									
Endocrine System																									
Adrenal gland																									
Adrenal gland, cortex																									
Pituitary gland							+		+							+					+	+			
Adenoma							X		X							X					X	X			
Thyroid gland																									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ovary				+		+	+	+	+		+						+	+				+	+	+	+
Choriocarcinoma																									
Granulosa cell tumor malignant																									
Granulosa cell tumor benign				X																					
Histiocytic sarcoma																									
Uterus		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Hematopoietic System																									
Bone marrow		+	+				+					+	+			+	+	+					+		+
Lymph node	+		+		+			+			+														
Axillary, sarcoma, metastatic																									
Iliac, histiocytic sarcoma																									
Mediastinal, fibrosarcoma, metastatic, skin																									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	4 1 4	4 2 1	4 3 2	4 4 1	4 4 4	4 5 5	4 6 3	4 7 2	4 8 2	4 8 5	**Total Tissues/ Tumors**
Alimentary System											
Gallbladder				+							1
Intestine small											1
Intestine small, jejunum											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Granulosa cell tumor malignant, metastatic, ovary											1
Hepatocellular carcinoma											1
Hepatocellular adenoma											1
Histiocytic sarcoma											2
Mesentery				+			+				7
Histiocytic sarcoma											1
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Cardiovascular System											
Blood vessel							+				1
Heart	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma, metastatic, skin											1
Histiocytic sarcoma											1
Endocrine System											
Adrenal gland											1
Adrenal gland, cortex											1
Pituitary gland											6
Adenoma											6
Thyroid gland											1
Follicular cell, adenoma											1
General Body System											
None											
Genital System											
Ovary	+		+					+		+	24
Choriocarcinoma											1
Granulosa cell tumor malignant											1
Granulosa cell tumor benign											1
Histiocytic sarcoma											1
Uterus	+	+	+		+	+		+	+	+	43
Histiocytic sarcoma											1
Hematopoietic System											
Bone marrow	+		+		+	+		+		+	21
Lymph node		+									19
Axillary, sarcoma, metastatic											1
Iliac, histiocytic sarcoma											1
Mediastinal, fibrosarcoma, metastatic, skin											1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	2 5 3	3 1 0	3 9 0	5 0 3	5 4 5	5 4 5	5 8 7	5 9 0	5 9 1	6 1 4	6 3 6	6 4 0	6 4 7	6 4 1	6 5 1	6 5 6	6 7 5	6 9 7	7 0 1	7 0 3	7 0 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 2 2	4 6 1	4 1 1	3 7 1	4 3 1	4 6 2	3 9 1	4 1 3	3 1 8	3 8 5	3 9 3	4 5 2	4 7 4	4 7 1	4 5 4	4 4 5	4 7 3	3 9 5	3 7 2	3 7 5	3 9 2	3 9 4	4 0 2	4 0 4	4 2 4
Hematopoietic System (continued)																									
Lymph node (continued)																									
Pancreatic, histiocytic sarcoma																				X					
Renal, histiocytic sarcoma																				X					
Lymph node, mesenteric			+	+		+	+		+	+	+						+			+					+
Histiocytic sarcoma																				X					
Spleen			+			+		+	+	+	+	+			+	+			+	+			+		+
Histiocytic sarcoma								X																	
Thymus									+	+							+								
Integumentary System																									
Mammary gland																	+		+				+		
Adenocarcinoma																							X		
Skin			+	+	+	+	+		+		+			+	+	+	+	+		+			+	+	+
Fibrosarcoma					X											X									
Sarcoma							X																		
Musculoskeletal System																									
Bone																		+							
Skeletal muscle				+													+								
Nervous System																									
Brain																	+								
Respiratory System																									
Lung			+		+			+		+	+	+					+		+	+			+		+
Alveolar/bronchiolar adenoma											X												X		
Alveolar/bronchiolar carcinoma																									X
Fibrosarcoma, metastatic, skin					X																				
Histiocytic sarcoma								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Urinary System																									
Kidney						+				+							+			+					
Histiocytic sarcoma																				X					
Ureter				+																					
Urinary bladder																	+								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X												X					
Lymphoma malignant lymphocytic			X														X		X						
Lymphoma malignant mixed				X		X			X		X	X													X
Lymphoma malignant undifferentiated cell type										X															

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731
Carcass ID Number	43 3	43 5	44 3	45 1	46 5	47 3	47 5	48 1	48 4	47 4	48 1	48 2	48 4	40 5	41 5	42 3	42 5	43 4	44 2	45 3	46 4	48 3	40 1	40 3	41 2
Hematopoietic System (continued)																										
Lymph node (continued)																										
Pancreatic, histiocytic sarcoma																										
Renal, histiocytic sarcoma																										
Lymph node, mesenteric	+										+															
Histiocytic sarcoma																										
Spleen	+	+			+		+		+		+				+							+	+		+	
Histiocytic sarcoma																										
Thymus																										
Integumentary System																										
Mammary gland																										
Adenocarcinoma																										
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Fibrosarcoma																										
Sarcoma																										
Musculoskeletal System																										
Bone																										
Skeletal muscle																										
Nervous System																										
Brain																										
Respiratory System																										
Lung			+										+		+											
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																										
Fibrosarcoma, metastatic, skin																										
Histiocytic sarcoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+																									
Histiocytic sarcoma																										
Ureter																										
Urinary bladder																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed	X	X			X			X		X	X								X			X				
Lymphoma malignant undifferentiated cell type																										

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 50 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	4 1 4	4 2 1	4 3 2	4 4 1	4 4 4	4 5 5	4 6 3	4 7 2	4 8 2	4 8 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)											
Lymph node (continued)											
Pancreatic, histiocytic sarcoma											1
Renal, histiocytic sarcoma											1
Lymph node, mesenteric											12
Histiocytic sarcoma											1
Spleen				+							25
Histiocytic sarcoma											1
Thymus											3
Integumentary System											
Mammary gland		+									4
Adenocarcinoma		X									2
Skin	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma											2
Sarcoma											1
Musculoskeletal System											
Bone											1
Skeletal muscle											2
Nervous System											
Brain											1
Respiratory System											
Lung											14
Alveolar/bronchiolar adenoma											2
Alveolar/bronchiolar carcinoma											1
Fibrosarcoma, metastatic, skin											1
Histiocytic sarcoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Special Senses System											
Eye											1
Urinary System											
Kidney											5
Histiocytic sarcoma											1
Ureter											1
Urinary bladder											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Lymphoma malignant lymphocytic											3
Lymphoma malignant mixed				X							14
Lymphoma malignant undifferentiated cell type											1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg

Number of Days on Study	0 3 2	0 6 6	1 0 0	1 3 7	1 8 2	1 8 2	1 8 2	1 9 1	5 8 4	6 4 0	6 4 5	6 6 4	6 7 2	7 1 7	7 2 3	7 2 5	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 2 9
Carcass ID Number	6 8 1	6 1 1	6 7 1	6 5 1	6 5 2	6 5 3	6 8 2	6 3 1	6 6 1	6 9 3	7 1 4	6 7 3	6 9 2	6 3 3	6 6 2	6 2 2	6 2 1	6 2 4	6 2 5	6 3 4	6 3 5	6 4 5	6 5 4	6 6 3	6 6 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	M	M	+	M	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	A	+	+	+	M	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	A	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Intestine small, jejunum	A	+	+	+	A	+	A	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma													X												
Mesentery									+				+			+								+	+
Histiocytic sarcoma													X												
Sarcoma, metastatic, uterus																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Sarcoma, metastatic, uterus																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Tooth																+									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	030	030	030	030	030	030	030	030	030	030	030	030	030	030	030	031	031	031
Carcass ID Number	68 44	69 41	69 44	69 45	71 53	72 33	72 44	61 22	61 33	62 33	63 22	64 22	64 44	67 42	77 25	68 33	68 55	70 11	70 33	70 44	71 11	72 12	61 24	61 15	64 11
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Histiocytic sarcoma																									
Mesentery						+			+		+			+	+				+			+			
Histiocytic sarcoma																									
Sarcoma, metastatic, uterus																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Sarcoma, metastatic, uterus																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Tooth																									+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	6 4 3	6 5 5	6 6 4	6 7 4	7 0 2	7 0 5	7 1 2	7 1 5	7 2 1	7 2 5	**Total Tissues/ Tumors**
Alimentary System											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	M	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma											1
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	53
Histiocytic sarcoma											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	54
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	54
Histiocytic sarcoma											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	54
Histiocytic sarcoma											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular adenoma			X			X					2
Histiocytic sarcoma											1
Mesentery	+	+		+	+						16
Histiocytic sarcoma											1
Sarcoma, metastatic, uterus											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Sarcoma, metastatic, uterus											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Papilloma squamous						X					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Tooth											2
Cardiovascular System											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	0 3 2	0 6 6	1 0 0	1 3 7	1 8 2	1 8 2	1 8 2	1 9 1	5 8 4	6 4 0	6 4 5	6 6 4	6 7 2	7 1 7	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 8 1	6 1 1	6 7 1	6 5 1	6 5 2	6 5 3	6 8 2	6 3 1	6 6 1	6 9 3	7 1 4	6 7 3	6 9 2	6 3 3	6 6 2	6 2 2	6 2 1	6 2 4	6 2 5	6 3 4	6 3 5	6 4 5	6 5 4	6 6 3	6 6 5
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma benign																X								
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	I
Adenoma																								
Pars intermedia, adenoma										X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X											
Follicular cell, adenoma										X														
General Body System																								
None																								
Genital System																								
Clitoral gland	+		+																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus			X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																	X				
Hemangioma																								
Leiomyosarcoma																								
Sarcoma																X								
Endometrium, histiocytic sarcoma																								
Vagina																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor NOS																								
Lymph node	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, histiocytic sarcoma													X											
Inguinal, histiocytic sarcoma													X											
Mediastinal, histiocytic sarcoma													X											
Renal, histiocytic sarcoma													X											
Lymph node, mesenteric	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X											
Sarcoma, metastatic, uterus																X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X	X											
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	M	M	M	M	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731
Carcass ID Number	6841	6891	6894	6895	7013	7123	7224	6212	6613	6623	6632	6642	6644	6642	6775	6785	6883	6905	7013	7044	7111	7212	6214	6845	6941
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	M	+	+	M	M	+	+	+	+	M	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X			X		X				X							X						
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Follicular cell, adenoma																		X							
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Hemangioma			X																						
Leiomyosarcoma																							X		
Sarcoma																									
Endometrium, histiocytic sarcoma							X																		
Vagina																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor NOS																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, histiocytic sarcoma																									
Inguinal, histiocytic sarcoma																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Sarcoma, metastatic, uterus																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	6 4 3	6 5 5	6 6 4	6 7 4	7 0 2	7 0 5	7 1 2	7 1 5	7 2 1	7 2 5	**Total Tissues/ Tumors**
Endocrine System											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Pheochromocytoma benign											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	+	+	+	+	M	M	+	+	+	M	43
Pituitary gland	+	+	+	+	+	+	+	M	+	+	57
Adenoma			X							X	7
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Follicular cell, adenoma											2
General Body System											
None											
Genital System											
Clitoral gland											2
Ovary	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, uterus											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma											2
Hemangioma											1
Leiomyosarcoma											1
Sarcoma											1
Endometrium, histiocytic sarcoma											1
Vagina					+	+		+			3
Hematopoietic System											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Plasma cell tumor NOS								X			1
Lymph node	+	+	+	+	+	+	+	+	+	+	58
Iliac, histiocytic sarcoma											1
Inguinal, histiocytic sarcoma											1
Mediastinal, histiocytic sarcoma											1
Renal, histiocytic sarcoma											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	58
Histiocytic sarcoma											1
Sarcoma, metastatic, uterus											1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											2
Thymus	+	M	+	+	+	+	+	+	+	+	53

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	0 3 2	0 6 6	1 0 0	1 3 7	1 8 2	1 8 2	1 8 2	1 9 1	5 8 4	6 4 0	6 4 5	6 6 4	6 7 2	7 1 7	7 2 3	7 2 5	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 2 9
Carcass ID Number	6 8 1	6 1 1	6 7 1	6 5 1	6 5 2	6 5 3	6 8 2	6 3 1	6 6 1	6 9 3	7 1 4	6 7 3	6 9 2	6 3 3	6 6 2	6 2 2	6 2 1	6 2 4	6 2 5	6 3 4	6 3 5	6 4 5	6 5 4	6 6 3	6 6 5
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenocarcinoma, multiple																				X					
Histiocytic sarcoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Adenocarcinoma, metastatic, uterus			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Histiocytic sarcoma													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Special Senses System																									
Eye																			+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus			X																						
Histiocytic sarcoma												X	X												
Urinary bladder	+	+	M	+	+	+	+	A	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Sarcoma, metastatic, uterus																X									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X	X												
Lymphoma malignant mixed										X	X			X							X			X	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731
Carcass ID Number	6844	6891	6994	6995	7013	7223	7224	6112	6113	6233	6322	6422	6444	6772	6775	6883	6885	7001	7003	7004	7011	7212	6124	6145	6441
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenocarcinoma, multiple																										
Histiocytic sarcoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma		X																								
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																								
Adenocarcinoma, metastatic, uterus																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																X				
Histiocytic sarcoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																										
Histiocytic sarcoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Sarcoma, metastatic, uterus																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																				
Lymphoma malignant mixed		X				X					X	X										X		X		

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid: 100 mg/kg (continued)

Number of Days on Study	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	
Carcass ID Number	6 4 3	6 5 5	6 6 4	6 7 4	7 0 2	7 0 5	7 1 2	7 1 5	7 2 1	7 2 5	**Total Tissues/ Tumors**
Integumentary System											
Mammary gland	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma			X								1
Adenocarcinoma, multiple											1
Histiocytic sarcoma											1
Skin	+	+	+	+	+	+	+	+	+	+	60
Fibrosarcoma											1
Musculoskeletal System											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											2
Adenocarcinoma, metastatic, uterus											1
Nervous System											
Brain	+	+	+	+	+	+	+	+	+	+	60
Spinal cord											2
Respiratory System											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											2
Histiocytic sarcoma											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Special Senses System											
Eye											1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, uterus											1
Histiocytic sarcoma											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	56
Histiocytic sarcoma											1
Sarcoma, metastatic, uterus											1
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											3
Lymphoma malignant mixed				X		X					13

TABLE D3
Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Histiocytic Sarcoma			
Overall rates[a]	3/60 (5%)	2/60 (3%)	1/59 (2%)
Adjusted rates[b]	6.2%	4.3%	2.1%
Terminal rates[c]	1/42 (2%)	0/40 (0%)	0/43 (0%)
First incidence (days)	513	590	672
Life table tests[d]	P=0.238N	P=0.531N	P=0.318N
Logistic regression tests[d]	P=0.206N	P=0.477N	P=0.297N
Cochran-Armitage test[d]	P=0.228N		
Fisher exact test[d]		P=0.500N	P=0.316N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	0/60 (0%)	3/14 (21%)	2/60 (3%)
Adjusted rates	0.0%	–[f]	4.5%
Terminal rates	0/42 (0%)	–	2/44 (5%)
First incidence (days)	–[e]	–	729 (T)
Life table tests			P=0.249
Logistic regression tests			P=0.249
Fisher exact test			P=0.248
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma			
Overall rates	5/55 (9%)	6/6 (100%)	7/57 (12%)
Adjusted rates	11.9%	–	17.1%
Terminal rates	4/41 (10%)	–	7/41 (17%)
First incidence (days)	724	–	729 (T)
Life table tests			P=0.382
Logistic regression tests			P=0.375
Fisher exact test			P=0.406
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	29/60 (48%)	18/60 (30%)	13/60 (22%)
Adjusted rates	55.4%	35.2%	27.3%
Terminal rates	19/42 (45%)	9/40 (23%)	10/44 (23%)
First incidence (days)	625	390	640
Life table tests	P=0.003N	P=0.085N	P=0.003N
Logistic regression tests	P=0.003N	P=0.033N	P=0.004N
Cochran-Armitage test	P=0.001N		
Fisher exact test		P=0.030N	P=0.002N
All Organs: Benign Tumors			
Overall rates	14/60 (23%)	11/60 (18%)	13/60 (22%)
Adjusted rates	32.6%	25.7%	28.1%
Terminal rates	13/42 (31%)	9/40 (23%)	11/44 (25%)
First incidence (days)	724	636	640
Life table tests	P=0.412N	P=0.381N	P=0.448N
Logistic regression tests	P=0.504N	P=0.424N	P=0.533N
Cochran-Armitage test	P=0.455N		
Fisher exact test		P=0.327N	P=0.500N

TABLE D3
Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid
(continued)

	Vehicle Control	50 mg/kg	100 mg/kg
All Organs: Malignant Tumors			
Overall rates	36/60 (60%)	27/60 (45%)	20/60 (33%)
Adjusted rates	64.2%	47.4%	38.9%
Terminal rates	22/42 (52%)	11/40 (28%)	13/44 (30%)
First incidence (days)	511	253	100
Life table tests	P=0.010N	P=0.200N	P=0.008N
Logistic regression tests	P=0.003N	P=0.053N	P=0.006N
Cochran-Armitage test	P=0.002N		
Fisher exact test		P=0.072N	P=0.003N
All Organs: Benign and Malignant Tumors			
Overall rates	41/60 (68%)	33/60 (55%)	27/60 (45%)
Adjusted rates	73.2%	58.3%	52.7%
Terminal rates	27/42 (64%)	17/40 (43%)	20/44 (45%)
First incidence (days)	511	253	100
Life table tests	P=0.021N	P=0.255N	P=0.017N
Logistic regression tests	P=0.011N	P=0.085N	P=0.021N
Cochran-Armitage test	P=0.007N		
Fisher exact test		P=0.094N	P=0.008N

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Incomplete histopathology in low dose group; no statistical analysis performed.

TABLE D4a
Historical Incidence of Squamous Cell Papillomas of the Forestomach in Female B6C3F$_1$ Mice Receiving Water Vehicle by Gavage

	Incidence in Controls Squamous Cell Papilloma
Overall Historical Incidence[a]	
Total	7/544 (1.3%)
Standard deviation	2.1%
Range	0%-6%

[a] Toxicology Data Management System compilation (data as of 22 December 1989), and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990). No historical control data were available for water gavage studies conducted at the International Research and Development Corporation.

TABLE D4b
Historical Incidence of Malignant Lymphomas in Female B6C3F$_1$ Mice Receiving Water Vehicle by Gavage

	Incidence in Controls Malignant Lymphoma
Overall Historical Incidence[a]	
Total	195/555 (35.1%)
Standard deviation	8.17%
Range	24%-52%

[a] Toxicology Data Management System compilation (data as of 22 December 1989), and Carcinogenesis Bioassay Data System compilation (data as of 6 March 1990). No historical control data were available for water gavage studies conducted at the International Research and Development Corporation.

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid

	Vehicle Control	50 mg/kg	100 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
Early deaths			
Dead	9	12	9
Moribund	8	8	4
Accidental deaths	1	0	3
Survivors			
Terminal sacrifice	41	40	44
Dead	1	0	0
Animals examined microscopically	60	60	60
Alimentary System			
Gallbladder	(55)	(1)	(51)
Calculus micro observation only	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Epithelium, hyperplasia	1 (2%)		
Intestine large, colon	(59)		(60)
Parasite metazoan	6 (10%)		3 (5%)
Intestine large, rectum	(60)		(58)
Hemorrhage	2 (3%)		
Inflammation, acute, focal	1 (2%)		
Ulcer, acute			1 (2%)
Intestine small, ileum	(52)		(54)
Amyloid deposition	1 (2%)		1 (2%)
Congestion	1 (2%)		
Inflammation, acute			1 (2%)
Intestine small, jejunum	(52)	(1)	(54)
Ulcer, acute			1 (2%)
Peyer's patch, hyperplasia, lymphoid	1 (2%)	1 (100%)	
Liver	(60)	(60)	(60)
Basophilic focus			1 (2%)
Hematopoietic cell proliferation granulocytic		1 (2%)	5 (8%)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	6 (10%)	17 (28%)	14 (23%)
Inflammation, chronic active		1 (2%)	1 (2%)
Necrosis, coagulative	3 (5%)	1 (2%)	
Pigmentation		1 (2%)	
Bile duct, hyperplasia			1 (2%)
Hepatocyte, necrosis		1 (2%)	
Mesentery	(23)	(7)	(16)
Inflammation, acute			1 (6%)
Inflammation, chronic	11 (48%)	2 (29%)	8 (50%)
Artery, adventitia, inflammation, chronic active		1 (14%)	
Pancreas	(60)		(60)
Atrophy	2 (3%)		4 (7%)
Clear cell focus			1 (2%)
Inflammation, chronic	1 (2%)		5 (8%)
Duct, cyst	2 (3%)		2 (3%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Alimentary System (continued)			
Salivary glands	(59)		(60)
Inflammation, chronic			3 (5%)
Mucocele			1 (2%)
Stomach, forestomach	(60)	(59)	(60)
Cyst		1 (2%)	
Diverticulum	1 (2%)		
Hyperkeratosis			4 (7%)
Hyperplasia, squamous, diffuse			1 (2%)
Hyperplasia, squamous, focal	5 (8%)	8 (14%)	12 (20%)
Hyperplasia, squamous, multifocal			3 (5%)
Inflammation, acute			1 (2%)
Inflammation, acute, multifocal			1 (2%)
Inflammation, chronic		3 (5%)	3 (5%)
Ulcer	2 (3%)		2 (3%)
Ulcer, multifocal		1 (2%)	1 (2%)
Vein, dilatation		1 (2%)	
Stomach, glandular	(57)	(60)	(60)
Erosion	3 (5%)	2 (3%)	2 (3%)
Hyperplasia, atypical, focal			1 (2%)
Hyperplasia, cystic	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Mineralization		1 (2%)	
Tooth	(2)		(2)
Developmental malformation			1 (50%)
Peridontal tissue, cyst			1 (50%)
Peridontal tissue, inflammation, acute			1 (50%)
Cardiovascular System			
Blood vessel	(57)	(1)	(60)
Inflammation, acute	1 (2%)		
Inflammation, chronic active		1 (100%)	
Heart	(60)	(60)	(60)
Degeneration	3 (5%)	2 (3%)	5 (8%)
Inflammation, chronic		1 (2%)	
Mineralization	1 (2%)		3 (5%)
Coronary artery, inflammation, chronic			1 (2%)
Valve, pigmentation	8 (13%)	20 (33%)	
Endocrine System			
Adrenal gland, cortex	(59)	(1)	(60)
Angiectasis			1 (2%)
Basophilic focus	1 (2%)		
Fibrosis, focal			1 (2%)
Hematopoietic cell proliferation granulocytic	1 (2%)		4 (7%)
Hemorrhage			1 (2%)
Hyperplasia			1 (2%)
Hypertrophy			4 (7%)
Inflammation, chronic	1 (2%)		
Necrosis	1 (2%)		2 (3%)
Subcapsular, hyperplasia	59 (100%)		58 (97%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(57)		(59)
Hyperplasia, focal	1 (2%)		
Parathyroid gland	(34)		(43)
Cyst			1 (2%)
Pituitary gland	(55)	(6)	(57)
Cyst	5 (9%)		3 (5%)
Hyperplasia, focal	16 (29%)		9 (16%)
Hypertrophy, focal			1 (2%)
Thyroid gland	(60)	(1)	(60)
Cyst	1 (2%)		
Inflammation, acute, focal	1 (2%)		
Inflammation, chronic	2 (3%)		2 (3%)
Pigmentation, cholesterol	1 (2%)		
Follicle, cyst	9 (15%)		2 (3%)
Follicular cell, hyperplasia	1 (2%)		5 (8%)
General Body System			
None			
Genital System			
Clitoral gland			(2)
Cyst			1 (50%)
Ovary	(59)	(24)	(60)
Abscess			3 (5%)
Cyst	24 (41%)	12 (50%)	25 (42%)
Cyst, multiple	11 (19%)	6 (25%)	10 (17%)
Inflammation, acute		1 (4%)	1 (2%)
Inflammation, chronic	2 (3%)		
Mineralization	1 (2%)	1 (4%)	2 (3%)
Artery, amyloid deposition	1 (2%)		
Uterus	(60)	(43)	(60)
Abscess			2 (3%)
Inflammation, acute		3 (7%)	2 (3%)
Thrombus			1 (2%)
Endometrium, hyperplasia, cystic	56 (93%)	41 (95%)	45 (75%)
Hematopoietic System			
Bone marrow	(60)	(21)	(60)
Myelofibrosis	26 (43%)	21 (100%)	22 (37%)
Myeloid cell, hyperplasia	3 (5%)		4 (7%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System (continued)			
Lymph node	(60)	(19)	(58)
Iliac, fibrosis			1 (2%)
Iliac, hematopoietic cell proliferation granulocytic			1 (2%)
Iliac, hyperplasia, plasma cell	1 (2%)	1 (5%)	
Iliac, inflammation, acute	1 (2%)		1 (2%)
Iliac, inflammation, chronic active			1 (2%)
Iliac, pigmentation			1 (2%)
Inguinal, inflammation, acute			1 (2%)
Mandibular, abscess	1 (2%)		
Mandibular, hyperplasia, lymphoid	2 (3%)		1 (2%)
Mediastinal, hemorrhage	1 (2%)		
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, hyperplasia, plasma cell		1 (5%)	
Pancreatic, inflammation, acute			1 (2%)
Renal, inflammation, acute			2 (3%)
Lymph node, mesenteric	(60)	(12)	(58)
Hematopoietic cell proliferation granulocytic			1 (2%)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	3 (5%)		1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, granulomatous			1 (2%)
Spleen	(60)	(25)	(60)
Fibrosis		2 (8%)	
Granuloma, multiple	1 (2%)		
Hematopoietic cell proliferation granulocytic	3 (5%)	2 (8%)	5 (8%)
Hematopoietic cell proliferation erythrocytic	2 (3%)	1 (4%)	3 (5%)
Hyperplasia, lymphoid	9 (15%)	4 (16%)	17 (28%)
Hyperplasia, plasma cell	1 (2%)		1 (2%)
Inflammation, granulomatous			1 (2%)
Pigmentation		1 (4%)	
Thymus	(54)	(3)	(53)
Abscess, multifocal	1 (2%)		
Atrophy	5 (9%)		2 (4%)
Cyst	8 (15%)	1 (33%)	9 (17%)
Hyperplasia, lymphoid	1 (2%)		
Inflammation, acute	1 (2%)		
Necrosis			2 (4%)
Pigmentation, lipofuscin			1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Integumentary System			
Mammary gland	(59)	(4)	(60)
Fibrosis, focal			1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic	4 (7%)		
Acinus, hyperplasia	1 (2%)		
Duct, cyst	4 (7%)	1 (25%)	4 (7%)
Duct, hyperplasia, atypical	1 (2%)		
Skin	(60)	(50)	(60)
Acanthosis	5 (8%)	2 (4%)	1 (2%)
Fibrosis			1 (2%)
Granuloma	1 (2%)		
Hyperkeratosis			1 (2%)
Infiltration cellular, mast cell		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute, chronic			1 (2%)
Inflammation, chronic	3 (5%)	3 (6%)	2 (3%)
Parasite external	3 (5%)		3 (5%)
Ulcer, acute			1 (2%)
Musculoskeletal System			
Bone	(60)	(1)	(60)
Periosteum, inflammation, granulomatous	1 (2%)		
Skeletal muscle	(3)	(2)	(2)
Edema			1 (50%)
Fibrosis			1 (50%)
Nervous System			
Brain	(60)	(1)	(60)
Compression	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Mineralization	29 (48%)	1 (100%)	24 (40%)
Necrosis, focal	1 (2%)		
Pigmentation, cholesterol	1 (2%)		
Respiratory System			
Lung	(60)	(14)	(60)
Congestion	1 (2%)	1 (7%)	2 (3%)
Hemorrhage	3 (5%)		2 (3%)
Inflammation, acute, focal			2 (3%)
Inflammation, chronic		1 (7%)	1 (2%)
Alveolar epithelium, hyperplasia, focal	2 (3%)	2 (14%)	
Alveolus, crystals			1 (2%)
Alveolus, infiltration cellular, histiocytic		1 (7%)	2 (3%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Monochloroacetic Acid (continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Respiratory System			
Lung (continued)			
Artery, mineralization	1 (2%)		
Artery, media, hypertrophy	6 (10%)		9 (15%)
Bronchus, fibrosis			1 (2%)
Interstitium, fibrosis, multifocal			1 (2%)
Interstitium, inflammation, chronic, focal			1 (2%)
Perivascular, infiltration cellular, lymphocytic	8 (13%)	2 (14%)	22 (37%)
Pleura, inflammation, acute, focal			1 (2%)
Nose	(60)	(60)	(60)
Concretion		1 (2%)	
Congestion	2 (3%)		
Cyst			1 (2%)
Exudate	9 (15%)	15 (25%)	11 (18%)
Granuloma	1 (2%)		1 (2%)
Inflammation, acute	5 (8%)	15 (25%)	31 (52%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	2 (3%)	3 (5%)	5 (8%)
Mucosa, nasopharyngeal duct, hyperplasia	1 (2%)		
Mucosa, nasolacrimal duct, hyperplasia	32 (53%)	32 (53%)	39 (65%)
Nasolacrimal duct, hyperplasia			1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)		
Olfactory epithelium, metaplasia	2 (3%)	5 (8%)	17 (28%)
Trachea	(60)		(60)
Inflammation, acute			3 (5%)
Metaplasia, squamous			1 (2%)
Special Senses System			
Eye		(1)	(1)
Cornea, inflammation, chronic			1 (100%)
Urinary System			
Kidney	(60)	(5)	(60)
Cyst	1 (2%)		
Hydronephrosis	1 (2%)		
Inflammation, chronic	17 (28%)		21 (35%)
Mineralization			1 (2%)
Nephropathy	11 (18%)		12 (20%)
Renal tubule, epithelium, pigmentation			1 (2%)
Urinary bladder	(57)	(1)	(56)
Inflammation, chronic	4 (7%)		3 (5%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail in Haworth *et al.* (1983) and Mortelmans *et al.* (1986). Monochloroacetic acid, sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX), was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of test chemical. High dose was limited by toxicity. All assays were repeated.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants that was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

MOUSE LYMPHOMA PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1987) and follows the basic format of Clive *et al.* (1979). Monochloroacetic acid was supplied as a coded aliquot by Radian Corporation (Austin, TX). The highest dose was determined by solubility or toxicity, and did not exceed 800 μg/mL. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT) resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for one day, to THG for one day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were tested in triplicate. Treated cultures contained 6 x 10^6 cells in a 10 mL volume of medium. Incubation with study chemical continued for 4 hours, at which time the medium plus chemical was removed and the cells were resuspended in 20 mL of fresh medium and incubated for an additional 2 days to allow expression of the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3 x 10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{-/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered "positive", i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay is initially performed without S9; because a clearly positive response was obtained in the absence of S9 for monochloroacetic acid, the experiment with S9 was not performed.

Chinese Hamster Ovary Cytogenetics Assays

Testing was performed as reported by Galloway *et al.* (1985, 1987) and presented briefly below. Monochloroacetic acid was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of test chemical; the high dose was limited by toxicity or solubility.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the test chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no test chemical and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 12 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 100 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response (w+); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

DROSOPHILA MELANOGASTER PROTOCOL

The assay for gene mutation induction was performed as described in Zimmering *et al.* (1985). Monochloroacetic acid was supplied as a coded aliquot from Radian Corporation (Austin, TX). The study chemical was assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, the chemical was retested by injection into adult males.

To administer the chemical by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to provide an opening for the delivery of the test solution. Injection was performed either manually by attaching a rubber bulb to the opposite end of the pipette and forcing through sufficient solution (0.2-0.3 μl) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double-sided tape. The chemical was injected under the wing into the thorax with the aid of a dissecting microscope.

Toxicity tests attempted to set concentrations of study chemical at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10 to 20 flies/vial) to feed for 72 hours on a solution of monochloroacetic acid (400 ppm) dissolved in water. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of monochloroacetic acid (900 ppm) dissolved in water and were allowed to recover for 24 hours. Exposed males were mated with three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated as successively earlier post-meiotic stages. F_1 heterozygous females were allowed to mate with their siblings and were then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution). If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as occurring in vials that contained no wild-type males after 17 days; these were retested. The two experiments, utilizing feed and injection, resulted in the testing of approximately 10,000 treated and 13,000 control chromosomes.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater that 0.10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.01 and 0.05 but the frequency in the treatment group was between 0.10% and 0.15%, or (b) the P value was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

RESULTS

Monochloroacetic acid, at concentrations of 10 to 3,333 μg/plate, did not induce mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested with a preincubation protocol in the presence and in the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1; Mortelmans *et al.*, 1986). In the mouse lymphoma assay, monochloroacetic acid was positive for induction of trifluorothymidine resistance in L5178Y cells in the absence of S9 at 400 μg/mL and 800 μg/mL, concentrations which caused an acidic pH shift in the cultures (Table E2; McGregor *et al.*, 1987). The responses in the first and third trials were considered positive; the results of trial two were inconclusive because the highest nontoxic dose achieved was only 250 μg/mL and the relative total growth (65%) indicated that higher doses were possible. In cytogenetic tests with Chinese hamster ovary (CHO) cells, monochloroacetic acid induced sister chromatid exchanges (SCE) at concentrations of 160 and 500 μg/mL without S9; no induction of SCE was observed in CHO cells exposed to 50 to 1,600 μg/mL monochloroacetic acid in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E3; Galloway *et al.*, 1987). Monochloroacetic acid was negative for induction of chromosomal aberrations (Abs) in CHO cells with and without S9 (Table E4; Galloway *et al.*, 1987). Small, dose-related increases in Abs were observed in both trials; these were, however, not statistically significant. Monochloroacetic acid administered by feeding (400 ppm in water) did not induce sex-linked recessive lethal (SLRL) mutations in germ cells of male *Drosophila melanogaster* (Table E5). When administered by injection (900 ppm in water), monochloroacetic acid produced a small increase in mutation frequency (frequency in treatment group=0.13%), but these results were considered equivocal (P=0.06)(Table E5).

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

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	134 ± 3.8	135 ± 3.2	107 ± 5.7	109 ± 3.6	132 ± 6.4	136 ± 6.5
	10	128 ± 3.0	143 ± 5.5				
	33	124 ± 1.0	134 ± 5.2	107 ± 8.5		124 ± 3.1	
	100	120 ± 8.6	135 ± 14.3	119 ± 10.1	114 ± 3.3	123 ± 4.7	146 ± 7.7
	333	122 ± 2.0	135 ± 2.6	113 ± 5.8	110 ± 4.4	127 ± 3.8	131 ± 7.4
	1,000	130 ± 5.0[c]	131 ± 10.3	120 ± 0.0	116 ± 9.6	137 ± 3.5	139 ± 0.9
	2,000				113 ± 7.1		143 ± 6.4
	3,333			114 ± 13.9[c]	78 ± 8.5[c]	121 ± 8.7[c]	111 ± 7.8[c]
Trial Summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,326 ± 14.4	1,207 ± 21.9	1,147 ± 48.8	2,405 ± 109.4	2,094 ± 45.9	1,114 ± 51.1
TA1535	0	35 ± 1.5	21 ± 0.9	19 ± 3.2	9 ± 1.3	22 ± 5.2	10 ± 2.3
	10	31 ± 1.2	25 ± 4.7				
	33	29 ± 4.5	20 ± 1.2	18 ± 2.3		21 ± 1.0	
	100	35 ± 0.9	18 ± 1.0	18 ± 0.9	10 ± 1.3	17 ± 2.5	12 ± 2.1
	333	25 ± 2.0	12 ± 2.3	13 ± 2.3	9 ± 1.2	15 ± 3.2	9 ± 2.0
	1,000	19 ± 2.3[c]	9 ± 1.2	12 ± 1.5	8 ± 0.6	15 ± 1.5	12 ± 2.6
	2,000				0 ± 0.3		3 ± 0.9
	3,333			0 ± 0.0[c]	0 ± 0.0[c]	0 ± 0.0[c]	0 ± 0.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,555 ± 26.7	824 ± 10.2	115 ± 9.5	173 ± 7.8	46 ± 5.4	66 ± 0.7
TA1537	0	9 ± 1.2	7 ± 1.2	8 ± 2.0	9 ± 0.9	6 ± 1.2	11 ± 3.0
	10	5 ± 0.3	7 ± 0.9				
	33	7 ± 2.5	6 ± 1.5	8 ± 2.1		6 ± 0.9	
	100	9 ± 0.9	10 ± 1.2	9 ± 1.5	9 ± 1.5	9 ± 0.3	9 ± 1.8
	333	6 ± 0.3	7 ± 0.6	8 ± 1.7	7 ± 2.0	8 ± 2.2	10 ± 2.2
	1,000	8 ± 2.2	8 ± 0.3	6 ± 1.3	9 ± 2.2	6 ± 1.0	7 ± 0.6
	2,000				2 ± 0.7		1 ± 0.9
	3,333			0 ± 0.0[c]	0 ± 0.0[c]	0 ± 0.0[c]	0 ± 0.3[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		126 ± 14.8	225 ± 22.3	126 ± 3.5	313 ± 18.8	67 ± 2.7	104 ± 8.5
TA98	0	26 ± 1.3	23 ± 3.3	28 ± 3.8	30 ± 3.7	31 ± 4.4	28 ± 4.1
	10	22 ± 3.8	16 ± 1.9				
	33	24 ± 3.4	20 ± 1.2	28 ± 4.3		30 ± 3.4	
	100	25 ± 2.8	18 ± 2.0	32 ± 3.3	28 ± 3.8	27 ± 2.6	26 ± 3.8
	333	24 ± 3.5	17 ± 1.2	34 ± 1.5	28 ± 2.7	30 ± 3.2	28 ± 2.3
	1,000	21 ± 1.7	18 ± 1.5	30 ± 6.4	25 ± 1.7	20 ± 3.2	28 ± 3.0
	2,000				20 ± 4.3		18 ± 2.4
	3,333			7 ± 1.2	13 ± 1.9	9 ± 1.5[c]	9 ± 2.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,727 ± 40.8	1,614 ± 39.2	1,024 ± 88.6	2,657 ± 71.9	854 ± 3.9	941 ± 46.9

TABLE E1
Mutagenicity of Monochloroacetic Acid in *Salmonella typhimurium* (continued)

[a] Study performed at EG&G Mason Research Institute. These data and the detailed protocol are presented in Mortelmans *et al.* (1986). Cells and monochloroacetic acid or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity to 3,333 μg/plate; 0 μg/plate dose is the solvent control.
[b] Revertants are presented as mean ± the standard error from 3 plates.
[c] Slight toxicity
[d] 2-aminoanthracene was used for all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Monochloroacetic Acid[a]

Compound	Conc. (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Distilled water		93[c]	93	136	49	
		82	96	91	37	
		80	107	68	28	
		79	104	106	45	40
Ethylmethanesulfonate						
		76	62	688	302	
	250	66	58	688	347	325*
Monochloroacetic acid						
	50	94	81	121	43	
		84	85	123	49	46
	100	83	77	88	35	
		112	75	135	40	38
	200	84	74	181	72	
		89	75	127	47	60
	400[d]	52	15	239	153	
		55	15	149	90	122*
	800	67	19	275	137	
		80	28	218	90	114*
Trial 2						
Distilled water		61	106	93	51	
		56	113	80	48	
		71	88	97	46	
		71	93	84	40	46
Ethylmethanesulfonate						
		50	56	499	336	
	250	70	74	683	327	331*
Monochloroacetic acid						
	31.25	57	79	112	66	
		66	100	88	45	55
	62.5	49	82	86	59	
		61	98	97	53	56
	125	44	66	85	64	
		100	91	116	39	51
	250	64	59	108	57	
		77	73	141	61	59
	500	Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Monochloroacetic Acid (continued)

Compound	Conc. (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Distilled water						
		76	87	157	69	
		93	91	155	56	
		81	98	185	77	
		90	125	200	74	69
Ethylmethanesulfonate						
		84	64	685	271	
	250	66	81	609	306	288*
Monochloroacetic acid						
	100	77	80	166	72	
		77	77	178	77	
		75	82	170	76	75
	200	73	56	184	84	
		73	62	220	101	
		76	51	214	94	93
	400[d]	62	8	315	171	
		50	7	299	198	184*
	600[d]	Lethal				
		Lethal				
		Lethal				
		Lethal				

* Significant positive response (P≤0.05); occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is approximately equal to 1.6.

[a] Study performed at Inveresk Research International. These data and the experimental protocol are presented in detail by McGregor *et al.* (1987). The highest dose of monochloroacetic acid was limited by toxicity. Treatment flasks are plated in triplicate; the average of the three tests is presented in the table. Cells (6×10^6) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 $\times 10^6$ cells treated); MF = mutant fraction.

[c] Mean from three replicate plates of approximately 1/3 (3×10^6) cells each. All data are evaluated statistically for both trend and peak response (P≤0.05 for at least one of the three highest dose sets). Both responses must be significantly (P≤0.05) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

[d] Acidic pH shift

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Monochloroacetic Acid[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Increase over Solvent (%)[b]
-S9[c]								
Trial 1--Summary: Positive								
Distilled water		50	1042	383	0.36	7.7	26.0	
Triethylenemelamine	0.0150	50	1050	1442	1.37	28.8	26.0	273.63
Monochloroacetic acid	50	50	1047	436	0.41	8.7	26.0	13.29
	160	50	1046	519	0.49	10.4	26.0	34.99*
	500	50	1049	572	0.54	11.4	28.0	48.35*
								P<0.001[d]
+S9[e]								
Trial 1--Summary: Negative								
Distilled water		50	1042	408	0.39	8.2	26.0	
Cyclophosphamide	1.0	50	1046	910	0.86	18.2	26.0	122.19
Monochloroacetic acid	50	50	1045	424	0.40	8.5	26.0	3.62
	160	50	1042	428	0.41	8.6	26.0	4.90
	500	50	1046	423	0.40	8.5	26.0	3.28
	1600	50	1051	479	0.45	9.6	26.0	16.40
								P=0.021

* Positive (≥20% increase over solvent control)

[a] Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with monochloroacetic acid or solvent (medium) as described in [c] and [d] below, and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.

[b] Percentage increase in SCEs/chromosome of culture exposed to monochloroacetic acid relative to those of culture exposed to solvent.

[c] In the absence of S9, cells were incubated with monochloroacetic acid or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and Colcemid was added, and incubation was continued for 2 to 3 hours.

[d] Significance of relative SCEs/chromosome tested by linear regression vs. log of the dose

[e] In the presence of S9, cells were incubated with monochloroacetic acid or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Monochloroacetic Acid[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs[d]
Trial 1--Harvest time: 14.0 hours					**Trial 1**--Harvest time: 14.0 hours				
Summary: Negative					Summary: Negative				
Distilled water	100	2	0.02	2.0	Distilled water	100	1	0.01	1.0
Triethylenemelamine					Cyclophosphamide				
0.150	50	14	0.28	20.0	1.50	50	27	0.54	44.0
Monochloroacetic acid					Monochloroacetic acid				
50	100	3	0.03	3.0	160	100	4	0.04	4.0
160	100	5	0.05	5.0	500	100	6	0.06	5.0
500	100	8	0.08	8.0	1600	100	7	0.07	6.0
				P=0.016					P=0.034

[a] Study performed at Columbia University. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with monochloroacetic acid or solvent (medium) as indicated in [b] and [c]. Cells were arrested in the first metaphase by addition of Colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with monochloroacetic acid or solvent for 12 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with monochloroacetic acid or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 12 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Significance of percent cells with aberrations tested by linear regression trend test vs. log of the dose

TABLE E5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Monochloroacetic Acid[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total[b]
				Mating 1	Mating 2	Mating 3	
Feeding	400	27	10	1/2,463	2/1,738	1/965	4/5,166 (0.08%)
	0			3/3,060	9/2,972	6/2,679	18/8,711 (0.21%)
Injection	900	9	9	4/2,314	3/1,841	0/1,270	7/5,425 (0.13%)
	0			0/1,836	1/1,672	1/1,406	2/4,914 (0.04%)

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

[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials.

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

TABLE F1a
Organ Weights[a] for Rats in the 16-Day Gavage Studies of Monochloroacetic Acid

	Vehicle Control	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
Male						
n	5	5	5	5	5	4
Necropsy body wt.	198 ± 4	193 ± 3	191 ± 6	193 ± 4	195 ± 5	180 ± 6*
Brain	1.68 ± 0.04	1.72 ± 0.02	1.73 ± 0.06	1.68 ± 0.02	1.69 ± 0.01	1.66 ± 0.04
Heart	0.66 ± 0.05	0.64 ± 0.02	0.64 ± 0.02	0.65 ± 0.02	0.66 ± 0.03	0.57 ± 0.06
Kidney	0.76 ± 0.02	0.83 ± 0.01	0.76 ± 0.03	0.80 ± 0.00	0.81 ± 0.04	0.79 ± 0.04
Liver	9.66 ± 0.37	8.93 ± 0.39	7.60 ± 0.35**	9.03 ± 0.32[b]	8.28 ± 0.35	8.93 ± 0.33
Lung	1.00 ± 0.03	1.04 ± 0.02	0.97 ± 0.14	1.10 ± 0.04	1.02 ± 0.03	0.95 ± 0.03
Thymus	0.52 ± 0.07	0.51 ± 0.02	0.48 ± 0.03	0.54 ± 0.02	0.47 ± 0.02	0.39 ± 0.07
Female						
n	5	5	5	5	5	5
Necropsy body wt.	144 ± 5	144 ± 4	144 ± 2	144 ± 3	143 ± 4	141 ± 3
Brain	1.66 ± 0.02	1.61 ± 0.05	1.61 ± 0.05	1.65 ± 0.05	1.63 ± 0.02	1.62 ± 0.02
Heart	0.38 ± 0.09	0.48 ± 0.02	0.52 ± 0.03	0.48 ± 0.07	0.52 ± 0.00	0.39 ± 0.06
Kidney	0.54 ± 0.06	0.60 ± 0.04	0.56 ± 0.01	0.56 ± 0.02	0.57 ± 0.01	0.58 ± 0.02
Liver	6.74 ± 0.44	6.12 ± 0.39	5.26 ± 0.06*	6.50 ± 0.16	5.33 ± 0.15*	6.72 ± 0.33
Lung	0.88 ± 0.06	0.98 ± 0.12	0.87 ± 0.05	0.83 ± 0.17	0.83 ± 0.01	0.86 ± 0.05
Thymus	0.28 ± 0.04	0.40 ± 0.02	0.42 ± 0.02	0.39 ± 0.05	0.38 ± 0.01	0.39 ± 0.04

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are given in grams. Mean ± standard error.
[b] n=4

TABLE F1b
Organ-Weight-to-Body-Weight Ratios[a] for Rats in the 16-Day Gavage Studies of Monochloroacetic Acid

	Vehicle Control	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
Male						
n	5	5	5	5	5	4
Necropsy body wt.	198 ± 4	193 ± 3	191 ± 6	193 ± 4	195 ± 5	180 ± 6*
Brain	8.49 ± 0.20	8.96 ± 0.14	9.07 ± 0.10	8.71 ± 0.22	8.67 ± 0.21	9.25 ± 0.37
Heart	3.32 ± 0.22	3.31 ± 0.11	3.33 ± 0.08	3.36 ± 0.07	3.39 ± 0.15	3.12 ± 0.28
Kidney	3.84 ± 0.06	4.33 ± 0.09**	3.96 ± 0.06*	4.15 ± 0.08*	4.17 ± 0.10*	4.37 ± 0.17**
Liver	48.80 ± 1.98	46.40 ± 2.30	39.70 ± 0.57**	46.60 ± 1.04[b]	42.40 ± 0.82	49.70 ± 2.19
Lung	5.05 ± 0.13	5.39 ± 0.14	5.00 ± 0.58	5.70 ± 0.26	5.23 ± 0.16	5.26 ± 0.17
Thymus	2.65 ± 0.38	2.67 ± 0.13	2.51 ± 0.11	2.78 ± 0.13	2.42 ± 0.10	2.14 ± 0.34
Female						
n	5	5	5	5	5	5
Necropsy body wt.	144 ± 5	144 ± 4	144 ± 2	144 ± 3	143 ± 4	141 ± 3
Brain	11.60 ± 0.32	11.20 ± 0.28	11.20 ± 0.20	11.40 ± 0.22	11.40 ± 0.18	11.50 ± 0.23
Heart	2.59 ± 0.56	3.35 ± 0.05	3.63 ± 0.23	3.33 ± 0.50	3.67 ± 0.12	2.80 ± 0.44
Kidney	3.73 ± 0.35	4.16 ± 0.22	3.89 ± 0.07	3.86 ± 0.20	3.98 ± 0.09	4.09 ± 0.16
Liver	47.00 ± 3.05	42.40 ± 1.77	36.50 ± 0.83*	45.10 ± 1.30	37.40 ± 1.04	47.60 ± 2.08
Lung	6.13 ± 0.36	6.76 ± 0.63	6.06 ± 0.30	5.73 ± 1.12	5.86 ± 0.17	6.12 ± 0.28
Thymus	1.96 ± 0.27	2.83 ± 0.20	2.88 ± 0.14	2.70 ± 0.36	2.66 ± 0.14	2.76 ± 0.30

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ-weight-to-body weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] n=4

TABLE F2a
Organ Weights[a] for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid

	Vehicle Control	30 mg/kg	60 mg/kg
Male			
n	10	10	8
Necropsy body wt.	348 ± 9	351 ± 8	339 ± 6
Adrenal	61.40 ± 3.07	56.10 ± 0.95	53.37 ± 2.40*
Brain	1.74 ± 0.02	1.74 ± 0.03	1.77 ± 0.02
Heart	1.14 ± 0.03	1.10 ± 0.03	1.01 ± 0.03**
Kidney	1.10 ± 0.04	1.19 ± 0.03	1.19 ± 0.04
Liver	9.85 ± 0.34	10.65 ± 0.31	10.98 ± 0.26*
Lung	1.30 ± 0.09	1.43 ± 0.04	1.38 ± 0.03
R. Testis	1.51 ± 0.03	1.49 ± 0.03	1.51 ± 0.02
Thymus	0.26 ± 0.01	0.26 ± 0.01	0.25 ± 0.01
Female			
n	10	9	9
Necropsy body wt.	205 ± 5	204 ± 3	203 ± 6
Adrenal	56.20 ± 1.76	59.67 ± 1.74	58.56 ± 1.55
Brain	1.67 ± 0.03	1.67 ± 0.03	1.64 ± 0.03
Heart	0.76 ± 0.02	0.70 ± 0.02	0.69 ± 0.02*
Kidney	0.68 ± 0.01	0.68 ± 0.02	0.69 ± 0.02
Liver	5.25 ± 0.17	5.08 ± 0.37	5.80 ± 0.23
Lung	1.09 ± 0.03	1.04 ± 0.03	1.03 ± 0.04
Thymus	0.24 ± 0.02	0.23 ± 0.01	0.25 ± 0.01[b]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights are given in grams except adrenal, which is given in milligrams. Mean ± standard error.
[b] n=8

TABLE F2b
Organ-Weight-to-Body-Weight Ratios[a] for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid

	Vehicle Control	30 mg/kg	60 mg/kg
Male			
n	10	10	8
Necropsy body wt.	348 ± 9	351 ± 8	339 ± 6
Adrenal	0.18 ± 0.01	0.16 ± 0.00	0.16 ± 0.01
Brain	5.01 ± 0.10	4.97 ± 0.10	5.25 ± 0.12
Heart	3.29 ± 0.07	3.13 ± 0.07	2.97 ± 0.06**
Kidney	3.15 ± 0.06	3.40 ± 0.05*	3.53 ± 0.11**
Liver	28.30 ± 0.43	30.30 ± 0.43*	32.40 ± 0.75**
Lung	3.74 ± 0.26	4.07 ± 0.07	4.07 ± 0.09
R. Testis	4.36 ± 0.05	4.24 ± 0.06	4.45 ± 0.06
Thymus	0.75 ± 0.01	0.73 ± 0.03	0.73 ± 0.03
Female			
n	10	9	9
Necropsy body wt.	205 ± 5	204 ± 3	203 ± 6
Adrenal	0.27 ± 0.01	0.29 ± 0.01	0.29 ± 0.01
Brain	8.15 ± 0.16	8.20 ± 0.13	8.07 ± 0.17
Heart	3.69 ± 0.06	3.45 ± 0.06*	3.39 ± 0.07**
Kidney	3.31 ± 0.04	3.35 ± 0.07	3.38 ± 0.05
Liver	25.50 ± 0.37	25.00 ± 1.78	28.60 ± 1.04**
Lung	5.32 ± 0.06	5.11 ± 0.13	5.04 ± 0.09
Thymus	1.17 ± 0.08	1.13 ± 0.04	1.25 ± 0.10[b]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ-weight-to-body weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] n=8

TABLE F3a
Organ Weights[a] for Rats at the 6-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
n	10	10	10
Necropsy body wt.	433 ± 5	442 ± 8	422 ± 12
Brain	2.27 ± 0.05	2.33 ± 0.05	2.35 ± 0.03
Heart	1.20 ± 0.02	1.17 ± 0.03	1.18 ± 0.02
Kidney	3.25 ± 0.03	3.31 ± 0.06	3.30 ± 0.07
Female			
n	10	10	10
Necropsy body wt.	240 ± 5	246 ± 4	232 ± 3
Brain	2.25 ± 0.03	2.13 ± 0.04*	2.16 ± 0.02*
Heart	0.74 ± 0.02	0.73 ± 0.01	0.77 ± 0.01
Kidney	1.96 ± 0.05[b]	1.94 ± 0.03	1.83 ± 0.02*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Organ weights and body weights are given in grams. Mean ± standard error.
[b] n=9

TABLE F3b
Organ-Weight-to-Body-Weight Ratios[a] for Rats at the 6-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
n	10	10	10
Necropsy body wt.	433 ± 5	442 ± 8	422 ± 12
Brain	5.24 ± 0.16	5.29 ± 0.10	5.61 ± 0.17
Heart	2.77 ± 0.06	2.64 ± 0.04	2.82 ± 0.08
Kidney	7.52 ± 0.07	7.49 ± 0.06	7.86 ± 0.13*
Female			
n	10	10	10
Necropsy body wt.	240 ± 5	246 ± 4	232 ± 3
Brain	9.38 ± 0.13	8.69 ± 0.19*	9.31 ± 0.14
Heart	3.10 ± 0.08	2.97 ± 0.04	3.32 ± 0.04*
Kidney	8.25 ± 0.09[b]	7.91 ± 0.09*	7.87 ± 0.08**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] n=9

TABLE F4a
Organ Weights[a] for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
n	7	7	7
Necropsy body wt.	443 ± 10	459 ± 23	428 ± 8
Brain	2.01 ± 0.04	2.01 ± 0.05	1.97 ± 0.05
Heart	1.35 ± 0.03	1.38 ± 0.06	1.29 ± 0.05
Kidney	1.69 ± 0.04	1.69 ± 0.05	1.69 ± 0.03
Liver	13.56 ± 0.50	13.02 ± 0.62	13.20 ± 0.62
Female			
n	7	7	7
Necropsy body wt.	276 ± 7	278 ± 7	281 ± 6
Brain	1.84 ± 0.04	1.77 ± 0.05	1.82 ± 0.04
Heart	0.91 ± 0.02	0.88 ± 0.03	0.88 ± 0.03
Kidney	0.97 ± 0.03	0.99 ± 0.02	1.02 ± 0.03
Liver	7.84 ± 0.33	8.30 ± 0.39	8.01 ± 0.17

[a] Organ weights and body weights are given in grams. Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test.

TABLE F4b
Organ-Weight-to-Body-Weight Ratios[a] for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg
Male			
n	7	7	7
Necropsy body wt.	443 ± 10	459 ± 23	428 ± 8
Brain	4.56 ± 0.14	4.42 ± 0.12	4.61 ± 0.05
Heart	3.06 ± 0.12	3.03 ± 0.12	3.02 ± 0.09
Kidney	3.83 ± 0.12	3.71 ± 0.09	3.94 ± 0.06
Liver	30.60 ± 0.82	28.40 ± 0.73	30.80 ± 1.01
Female			
n	7	7	7
Necropsy body wt.	276 ± 7	278 ± 7	281 ± 6
Brain	6.70 ± 0.14	6.39 ± 0.19	6.49 ± 0.16
Heart	3.29 ± 0.08	3.16 ± 0.07	3.14 ± 0.05
Kidney	3.53 ± 0.07	3.58 ± 0.07	3.63 ± 0.11
Liver	28.40 ± 0.74	29.90 ± 1.09	28.50 ± 0.75

[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test.

TABLE F5a
Organ Weights[a] for Mice in the 16-Day Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	240 mg/kg
Male						
n	5	4	5	5	5	0
Necropsy body wt.	25.2 ± 1.0	22.8 ± 1.0	25.0 ± 0.8	24.4 ± 1.1	26.4 ± 1.1	–[b]
Brain	0.47 ± 0.01	0.43 ± 0.01	0.43 ± 0.02	0.46 ± 0.02	0.44 ± 0.01	–
Heart	0.13 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	–
Kidney	0.21 ± 0.01	0.20 ± 0.02	0.21 ± 0.01	0.21 ± 0.01	0.25 ± 0.02	–
Liver	1.35 ± 0.07	1.30 ± 0.11	1.28 ± 0.03	1.35 ± 0.08	1.54 ± 0.03*	–
Lung	0.20 ± 0.02	0.20 ± 0.01	0.19 ± 0.03	0.18 ± 0.02	0.18 ± 0.01	–
Thymus	0.05 ± 0.01	0.04 ± 0.00	0.04 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	–

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg	240 mg/kg	480 mg/kg
Female						
n	5	5	5	5	0	0
Necropsy body wt.	21.2 ± 0.4	20.0 ± 0.6	20.6 ± 0.8	20.8 ± 0.4	–[b]	–
Brain	0.46 ± 0.01	0.47 ± 0.01	0.45 ± 0.01	0.44 ± 0.01	–	–
Heart	0.12 ± 0.01	0.11 ± 0.01	0.10 ± 0.00	0.11 ± 0.01	–	–
Kidney	0.17 ± 0.01	0.14 ± 0.02	0.15 ± 0.01	0.16 ± 0.01	–	–
Liver	1.21 ± 0.04	1.16 ± 0.09	0.92 ± 0.04*	1.19 ± 0.06	–	–
Lung	0.19 ± 0.02	0.19 ± 0.01	0.19 ± 0.01	0.18 ± 0.02	–	–
Thymus	0.04 ± 0.01	0.06 ± 0.00	0.05 ± 0.01	0.06 ± 0.01	–	–

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ weights and body weights are given in grams. Mean ± standard error.
[b] No data reported due to 100% mortality in this group

TABLE F5b
Organ-Weight-to-Body-Weight Ratios[a] for Mice in the 16-Day Gavage Studies of Monochloroacetic Acid

	Vehicle Control	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	240 mg/kg
Male						
n	5	4	5	5	5	0
Necropsy body wt.	25.2 ± 1.0	22.8 ± 1.0	25.0 ± 0.8	24.4 ± 1.1	26.4 ± 1.1	–[b]
Brain	18.60 ± 0.68	18.80 ± 0.46	17.20 ± 1.07	18.90 ± 0.69	16.70 ± 0.70	–
Heart	4.97 ± 0.29	5.27 ± 0.35	4.74 ± 0.26	5.02 ± 0.32	4.94 ± 0.30	–
Kidney	8.24 ± 0.13	8.64 ± 0.43	8.25 ± 0.19	8.54 ± 0.39	9.40 ± 0.67	–
Liver	53.40 ± 1.58	56.90 ± 3.93	51.40 ± 2.11	55.50 ± 2.01	58.60 ± 1.39	–
Lung	8.10 ± 0.78	8.93 ± 0.35	7.37 ± 0.97	7.13 ± 0.53	6.94 ± 0.54	–
Thymus	1.84 ± 0.22	1.64 ± 0.19	1.43 ± 0.33	2.24 ± 0.26	1.87 ± 0.38	–

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg	240 mg/kg	480 mg/kg
Female						
n	5	5	5	5	0	0
Necropsy body wt.	21.2 ± 0.4	20.0 ± 0.6	20.6 ± 0.8	20.8 ± 0.4	–[b]	–
Brain	21.70 ± 0.51	23.90 ± 1.37	21.90 ± 0.67	21.30 ± 0.53	–	–
Heart	5.56 ± 0.57	5.58 ± 0.30	5.06 ± 0.16	5.28 ± 0.41	–	–
Kidney	8.24 ± 0.52	6.92 ± 0.80	7.13 ± 0.63	7.48 ± 0.61	–	–
Liver	57.00 ± 1.10	58.10 ± 4.12	44.60 ± 0.59*	57.20 ± 1.93	–	–
Lung	9.16 ± 0.75	9.37 ± 0.60	9.04 ± 0.42	8.63 ± 0.79	–	–
Thymus	2.07 ± 0.21	2.92 ± 0.26	2.55 ± 0.44	3.00 ± 0.39	–	–

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] No data reported due to 100% mortality in this group

TABLE F6a
Organ Weights[a] for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Male						
n	8	10	10	10	10	0
Necropsy body wt.	29.4 ± 0.5	31.2 ± 0.5	29.6 ± 0.9	30.0 ± 0.7	28.7 ± 0.6	–[b]
Adrenal	6.25 ± 0.53	8.22 ± 0.78[c]	7.50 ± 0.76	8.56 ± 0.97[c]	7.80 ± 0.68	–
Brain	0.43 ± 0.01	0.42 ± 0.02	0.42 ± 0.01	0.42 ± 0.01	0.42 ± 0.01	–
Heart	0.15 ± 0.00	0.16 ± 0.01	0.15 ± 0.01	0.16 ± 0.01	0.14 ± 0.01	–
Kidney	0.23 ± 0.01	0.22 ± 0.00	0.22 ± 0.01	0.22 ± 0.01	0.22 ± 0.01	–
Liver	1.05 ± 0.03	1.07 ± 0.03	1.04 ± 0.05	1.10 ± 0.04	1.03 ± 0.03	–
Lung	0.19 ± 0.00	0.18 ± 0.01	0.16 ± 0.00*	0.18 ± 0.01[c]	0.18 ± 0.01	–
R. Testis	0.11 ± 0.00[d]	0.11 ± 0.01	0.11 ± 0.00	0.11 ± 0.00	0.12 ± 0.00	–
Thymus	0.03 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	–
Female						
n	10	10	10	9	10	8
Necropsy body wt.	24.1 ± 0.6	23.6 ± 0.5	24.2 ± 0.4	24.7 ± 0.4	23.5 ± 0.5	23.6 ± 0.6
Adrenal	9.67 ± 0.73[c]	10.50 ± 0.43	12.52 ± 0.76	12.50 ± 0.78[e]	10.40 ± 0.45	9.12 ± 0.30
Brain	0.44 ± 0.01	0.45 ± 0.01	0.43 ± 0.01	0.45 ± 0.01	0.45 ± 0.01	0.43 ± 0.01
Heart	0.12 ± 0.00	0.13 ± 0.01	0.12 ± 0.00	0.13 ± 0.01	0.12 ± 0.01	0.11 ± 0.00
Kidney	0.15 ± 0.01	0.16 ± 0.00	0.16 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.16 ± 0.01
Liver	0.86 ± 0.03	0.87 ± 0.02	0.87 ± 0.05	0.94 ± 0.02*	0.87 ± 0.02	0.96 ± 0.03*
Lung	0.18 ± 0.01	0.18 ± 0.01	0.16 ± 0.00	0.18 ± 0.01	0.17 ± 0.01	0.16 ± 0.01
Thymus	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights are given in grams except adrenal, which is given in milligrams. Mean ± standard error.
[b] No data reported due to 100% mortality in this group
[c] n=9
[d] n=7
[e] n=8

TABLE F6b
Organ-Weight-to-Body-Weight Ratios[a] for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Male						
n	8	10	10	10	10	0
Necropsy body wt.	29.4 ± 0.5	31.2 ± 0.5	29.6 ± 0.9	30.0 ± 0.7	28.7 ± 0.6	–[b]
Adrenal	0.21 ± 0.02	0.26 ± 0.02[c]	0.26 ± 0.03	0.29 ± 0.03[c]	0.27 ± 0.02	–
Brain	14.70 ± 0.28	13.30 ± 0.59	14.30 ± 0.45	14.00 ± 0.39	14.70 ± 0.26	–
Heart	5.00 ± 0.17	5.06 ± 0.18	5.05 ± 0.19	5.19 ± 0.23	5.04 ± 0.13	–
Kidney	7.90 ± 0.26	7.15 ± 0.12*	7.60 ± 0.22	7.45 ± 0.17	7.83 ± 0.16	–
Liver	35.80 ± 0.54	34.20 ± 0.84	35.30 ± 1.16	36.40 ± 0.65	35.90 ± 0.74	–
Lung	6.48 ± 0.16	5.79 ± 0.25	5.56 ± 0.23*	6.15 ± 0.24[c]	6.13 ± 0.18	–
R. Testis	3.90 ± 0.10[d]	3.44 ± 0.20	3.83 ± 0.14	3.82 ± 0.07	4.06 ± 0.20	–
Thymus	0.89 ± 0.07	0.68 ± 0.07	0.82 ± 0.09	0.89 ± 0.08	0.90 ± 0.07	–
Female						
n	10	10	10	9	10	8
Necropsy body wt.	24.1 ± 0.6	23.6 ± 0.5	24.2 ± 0.4	24.7 ± 0.4	23.5 ± 0.5	23.6 ± 0.6
Adrenal	0.40 ± 0.03[c]	0.45 ± 0.02	0.52 ± 0.03	0.51 ± 0.03[e]	0.44 ± 0.02	0.39 ± 0.02
Brain	18.10 ± 0.39	19.10 ± 0.36	17.70 ± 0.43	18.10 ± 0.19	19.0 ± 0.32	18.40 ± 0.59
Heart	5.00 ± 0.13	5.50 ± 0.33	4.99 ± 0.19	5.29 ± 0.21	5.27 ± 0.15	4.65 ± 0.16
Kidney	6.27 ± 0.27	6.65 ± 0.14	6.44 ± 0.23	6.69 ± 0.21	6.78 ± 0.08	6.86 ± 0.24
Liver	35.70 ± 0.48	36.90 ± 0.58	36.00 ± 1.58	38.20 ± 0.77*	36.80 ± 0.41	40.50 ± 0.79**
Lung	7.26 ± 0.24	7.63 ± 0.21	6.74 ± 0.17	7.45 ± 0.31	7.45 ± 0.25	6.70 ± 0.33
Thymus	1.30 ± 0.08	1.43 ± 0.06	1.21 ± 0.11	1.30 ± 0.07	1.23 ± 0.07	1.44 ± 0.12

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ-weight-to-body-weight ratios are given as mg organ weight/g body weight. Mean ± standard error.
[b] No data reported due to 100% mortality in this group
[c] n=9
[d] n=7
[e] n=8

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid[a]

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Male[b]						
Hematology						
Hematocrit (%)						
4 weeks (P=0.039)	45.4 ± 0.7	46.1 ± 0.6	46.0 ± 0.7	44.3 ± 0.4	46.8 ± 0.5	47.8 ± 0.4*
8 weeks	45.2 ± 0.1	44.5 ± 1.0	44.1 ± 1.0	46.2 ± 0.8	48.4 ± 0.6[c]	–[d]
13 weeks	48.1 ± 0.4	48.9 ± 0.4	48.0 ± 1.0[e]	–	–	–
Hemoglobin (g/dL)						
4 weeks	17.5 ± 0.3	17.6 ± 0.2	17.8 ± 0.2	16.9 ± 0.1	17.8 ± 0.2	18.5 ± 0.2*
8 weeks	16.3 ± 0.1	15.9 ± 0.4	15.9 ± 0.3	16.7 ± 0.3	17.9 ± 0.1[c]	–
13 weeks	17.4 ± 0.2	17.6 ± 0.2	17.5 ± 0.4[e]	–	–	–
Erythrocytes ($10^6/\mu L$)						
4 weeks (P=0.035)	7.88 ± 0.13	8.03 ± 0.12	7.93 ± 0.10	7.67 ± 0.05	8.08 ± 0.05	8.43 ± 0.11**
8 weeks	7.52 ± 0.04	7.40 ± 0.14	7.33 ± 0.15	7.75 ± 0.14	8.23 ± 0.06[c]	–
13 weeks	7.94 ± 0.07	8.07 ± 0.07	7.92 ± 0.19[e]	–	–	–
Mean cell volume (fL)						
4 weeks (P=0.005)	57.8 ± 0.4	59.8 ± 0.2	58.2 ± 0.2	57.6 ± 0.2	57.8 ± 0.6	56.6 ± 0.5
8 weeks	60.0 ± 0.3	60.2 ± 0.4	60.2 ± 0.4	59.4 ± 0.2	59.0 ± 0.0[c]	–
13 weeks	60.5 ± 0.3	60.5 ± 0.2	60.8 ± 0.3[e]	–	–	–
Mean cell hemoglobin (pg)						
4 weeks	22.2 ± 0.1	22.0 ± 0.1	22.4 ± 0.1	22.1 ± 0.1	22.0 ± 0.2	21.9 ± 0.0
8 weeks	21.7 ± 0.1	21.6 ± 0.2	21.7 ± 0.1	21.6 ± 0.1	21.7 ± 0.1[c]	–
13 weeks	21.9 ± 0.1	21.9 ± 0.1	22.1 ± 0.1[e]	–	–	–
Mean cell hemoglobin concentration (g/dL)						
4 weeks	38.6 ± 0.2	38.2 ± 0.2	38.7 ± 0.2	38.2 ± 0.2	38.0 ± 0.3	38.7 ± 0.3
8 weeks	36.1 ± 0.2	35.8 ± 0.3	36.1 ± 0.3	36.1 ± 0.1	36.9 ± 0.4[c]	–
13 weeks	36.2 ± 0.1	36.1 ± 0.2	36.5 ± 0.1[e]	–	–	–
Leukocytes ($10^3/\mu L$)						
4 weeks	6.58 ± 0.72	7.24 ± 0.77	7.06 ± 0.51	7.08 ± 0.69	7.36 ± 0.37	7.40 ± 0.47
8 weeks	7.22 ± 0.16	6.04 ± 0.30*	6.68 ± 0.55	6.18 ± 0.54	4.85 ± 0.05*[c]	–
13 weeks	7.61 ± 0.37	7.28 ± 0.29	7.15 ± 0.43[e]	–	–	–
Segmented neutrophils ($10^3/\mu L$)						
4 weeks (P<0.001)	1.06 ± 0.12	1.53 ± 0.27	1.29 ± 0.20	1.59 ± 0.22*	1.64 ± 0.10*	2.72 ± 0.44**
8 weeks (P=0.020)	0.96 ± 0.11	1.16 ± 0.11	1.24 ± 0.22	1.97 ± 0.46	1.65 ± 0.08[c]	–
13 weeks	1.75 ± 0.17	1.59 ± 0.18	1.46 ± 0.15[e]	–	–	–
Lymphocytes ($10^3/\mu L$)						
4 weeks	5.37 ± 0.61	5.52 ± 0.58	5.50 ± 0.56	5.19 ± 0.68	5.55 ± 0.36	4.43 ± 0.48
8 weeks (P<0.001N)	5.99 ± 0.27	4.59 ± 0.19**	5.16 ± 0.37*	3.93 ± 0.42**	3.01 ± 0.23**[c]	–
13 weeks	5.55 ± 0.27	5.44 ± 0.20	5.46 ± 0.41[e]	–	–	–
Monocytes ($10^3/\mu L$)						
4 weeks	0.13 ± 0.05	0.11 ± 0.05	0.20 ± 0.08	0.21 ± 0.06	0.08 ± 0.04	0.19 ± 0.06
8 weeks	0.25 ± 0.07	0.24 ± 0.03	0.21 ± 0.04	0.21 ± 0.03	0.15 ± 0.05[c]	–
13 weeks	0.17 ± 0.03	0.17 ± 0.04	0.16 ± 0.04[e]	–	–	–

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Male (continued)						
Hematology (continued)						
Eosinophils ($10^3/\mu L$)						
4 weeks	0.03 ± 0.02	0.06 ± 0.03	0.05 ± 0.03	0.08 ± 0.04	0.09 ± 0.03	0.06 ± 0.04
8 weeks	0.01 ± 0.01	0.05 ± 0.04	0.07 ± 0.02	0.05 ± 0.02	0.05 ± 0.05[c]	–
13 weeks (P=0.016)	0.14 ± 0.03	0.07 ± 0.02	0.05 ± 0.03*[e]	–	–	–
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
4 weeks (P<0.001)	14.6 ± 0.7	14.2 ± 0.6	15.9 ± 0.8	16.8 ± 0.3*	19.0 ± 0.3**	21.4 ± 1.4**
8 weeks (P<0.001)	15.0 ± 0.9	15.4 ± 0.5	17.7 ± 0.9	19.1 ± 1.0*	21.5 ± 0.3*[c]	–
13 weeks	14.0 ± 0.5	14.5 ± 0.3	15.0 ± 0.6[e]	–	–	–
Creatinine (mg/dL)						
4 weeks	0.48 ± 0.04	0.48 ± 0.02	0.50 ± 0.03	0.46 ± 0.02	0.50 ± 0.03	0.50 ± 0.00
8 weeks	0.62 ± 0.02	0.58 ± 0.04	0.58 ± 0.02	0.58 ± 0.02	0.55 ± 0.05[c]	–
13 weeks	0.62 ± 0.02	0.58 ± 0.01	0.59 ± 0.02[e]	–	–	–
Sodium (mEq/L)						
4 weeks	148 ± 0	150 ± 2	148 ± 1	148 ± 0	148 ± 0[f]	149 ± 2
8 weeks	148 ± 1	147 ± 1	147 ± 1	148 ± 1	146 ± 2[c]	–
13 weeks	149 ± 1	149 ± 1	148 ± 1[e]	–	–	–
Potassium (mEq/L)						
4 weeks	6.0 ± 0.1	6.2 ± 0.1	6.3 ± 0.2	6.4 ± 0.2	6.2 ± 0.2[f]	6.5 ± 0.2
8 weeks	5.6 ± 0.2	5.8 ± 0.2	5.8 ± 0.2	6.0 ± 0.1	6.1 ± 0.6[c]	–
13 weeks (P=0.047)	5.5 ± 0.1	5.8 ± 0.1*	5.8 ± 0.1[e]	–	–	–
Chloride (mEq/L)						
4 weeks	107 ± 1	107 ± 0	107 ± 1	107 ± 1	106 ± 1[f]	108 ± 1
8 weeks	106 ± 1	107 ± 0	106 ± 1	107 ± 1	106 ± 1[c]	–
13 weeks	105 ± 0	105 ± 1	105 ± 1[e]	–	–	–
Calcium (mg/dL)						
4 weeks	10.4 ± 0.0	10.5 ± 0.1	10.6 ± 0.1	10.3 ± 0.1	10.6 ± 0.1	10.2 ± 0.1
8 weeks	11.0 ± 0.2	10.8 ± 0.1	10.9 ± 0.2	10.9 ± 0.2	10.4 ± 0.4[c]	–
13 weeks	11.2 ± 0.2	11.2 ± 0.2	10.6 ± 0.1[e]	–	–	–
Phosphorus (mg/dL)						
4 weeks (P=0.002)	8.0 ± 0.5	7.9 ± 0.2	8.1 ± 0.1	8.3 ± 0.1	8.9 ± 0.5	9.4 ± 0.3*
8 weeks	6.7 ± 0.2	6.8 ± 0.2	7.1 ± 0.2	7.6 ± 0.3*	6.5 ± 0.6[c]	–
13 weeks (P=0.022)	7.5 ± 0.3	8.1 ± 0.3	8.2 ± 0.2[e]	–	–	–
Total protein (g/dL)						
4 weeks	6.8 ± 0.1	6.7 ± 0.1	6.7 ± 0.1	6.7 ± 0.	6.9 ± 0.1	6.7 ± 0.1
8 weeks	7.0 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	7.1 ± 0.2	6.5 ± 0.5[c]	–
13 weeks	6.6 ± 0.1	6.6 ± 0.1	6.7 ± 0.2[e]	–	–	–
Albumin (g/dL)						
4 weeks	3.7 ± 0.1	3.7 ± 0.0	3.7 ± 0.0	3.6 ± 0.0	3.8 ± 0.0	3.7 ± 0.0
8 weeks	3.6 ± 0.0	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.5 ± 0.2[c]	–
13 weeks	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.1[e]	–	–	–

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Male (continued)						
Clinical Chemistry (continued)						
Total bilirubin (mg/dL)						
4 weeks	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
8 weeks	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	–
13 weeks	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0[e]	–	–	–
A/G ratio						
4 weeks	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.3 ± 0.0
8 weeks	1.1 ± 0.0	1.0 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.2 ± 0.0[c]	–
13 weeks	1.1 ± 0.0	1.2 ± 0.0	1.2 ± 0.0[e]	–	–	–
Methemoglobin (%)						
4 weeks	4.17 ± 1.93	7.86 ± 1.53	6.80 ± 2.72	7.70 ± 1.77	4.83 ± 2.08	8.91 ± 1.67
8 weeks	2.83 ± 1.42	4.12 ± 0.66	0.81 ± 0.81	1.78 ± 0.55	0.80 ± 0.16[c]	–
13 weeks	4.60 ± 0.74	4.57 ± 0.85	3.22 ± 0.74[e]	–	–	–
Alanine aminotransferase (IU/L)						
4 weeks (P<0.001)	37 ± 1	38 ± 2	39 ± 1	38 ± 3	43 ± 3	52 ± 2**
8 weeks (P=0.013)	36 ± 1	36 ± 2	45 ± 3*	46 ± 4	43 ± 3[c]	–
13 weeks	36 ± 1	38 ± 1	38 ± 2[e]	–	–	–
Aspartate aminotransferase (IU/L)						
4 weeks (P=0.010)	106 ± 7	109 ± 6	109 ± 10	104 ± 7	121 ± 12	213 ± 26**
8 weeks (P=0.003)	78 ± 2	73 ± 2	89 ± 9	133 ± 20*	119 ± 1[c]	–
13 weeks	74 ± 3	72 ± 3	77 ± 4[e]	–	–	–
Lactate dehydrogenase (IU/L)						
4 weeks	961 ± 162	957 ± 140	1018 ± 208	884 ± 141	931 ± 124	959 ± 192
8 weeks	658 ± 64	597 ± 64	647 ± 73	725 ± 83	693 ± 38[c]	–
13 weeks	711 ± 71	660 ± 70	774 ± 80[e]	–	–	–
Ornithine carbamyltransferase (IU/L)						
4 weeks	3 ± 2[c]	2 ± 2[c]	–	3 ± 1[g]	3 ± 1	4 ± 2[g]
8 weeks	1 ± 0[g]	1 ± 0	2 ± 1[f]	1 ± 0[g]	–	–
13 weeks	1 ± 0[h]	3 ± 1[i]	1 ± 0[i]	–	–	–
Sorbitol dehydrogenase (IU/L)						
4 weeks	10 ± 0	9 ± 0	9 ± 1	9 ± 0	11 ± 1	11 ± 1
8 weeks	13 ± 1	19 ± 2	26 ± 3*	21 ± 3	12 ± 3[c]	–
13 weeks	15 ± 1	17 ± 1	15 ± 2[e]	–	–	–
Cholinesterase (IU/mL)						
4 weeks	0.9 ± 0.0	0.8 ± 0.0	0.9 ± 0.0	0.8 ± 0.0	0.8 ± 0.0	0.9 ± 0.0
8 weeks (P=0.034N)	0.9 ± 0.0	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.0*	0.8 ± 0.0[c]	–
13 weeks (P<0.001N)	0.8 ± 0.0	0.7 ± 0.0*	0.7 ± 0.0**[e]	–	–	–
Triiodothyronine (ng/dL)						
4 weeks	89 ± 6	91 ± 7	93 ± 3	98 ± 11	102 ± 8	90 ± 4
8 weeks	71 ± 6	–	–	73 ± 12	–	–
Thyroxin (μg/dL)						
4 weeks (P<0.001)	7 ± 1	7 ± 0	8 ± 0	8 ± 1*	10 ± 1**	9 ± 1**
8 weeks (P=0.022)	6 ± 0	–	–	9 ± 1*	–	–

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Female						
Hematology						
Hematocrit (%)						
4 weeks	45.0 ± 0.8	44.5 ± 1.0	47.0 ± 0.7	44.2 ± 1.3	45.5 ± 0.9	46.4 ± 1.4[g]
8 weeks	44.4 ± 0.7	44.7 ± 0.7[f]	44.5 ± 1.3	46.4 ± 0.5	-	-
13 weeks	49.3 ± 0.5	48.9 ± 0.4	49.3 ± 0.7[e]	-	-	-
Hemoglobin (g/dL)						
4 weeks	17.0 ± 0.3	17.1 ± 0.3	17.8 ± 0.1	16.7 ± 0.4	17.2 ± 0.4	17.8 ± 0.5[g]
8 weeks	15.8 ± 0.3	15.9 ± 0.3[f]	15.9 ± 0.4	16.5 ± 0.3	-	-
13 weeks	17.6 ± 0.2	17.7 ± 0.2[j]	17.8 ± 0.3[e]	-	-	-
Erythrocytes ($10^6/\mu L$)						
4 weeks	7.54 ± 0.10	7.65 ± 0.13	7.94 ± 0.07	7.47 ± 0.20	7.74 ± 0.15	7.97 ± 0.21[g]
8 weeks (P=0.046)	6.93 ± 0.10	7.04 ± 0.11[f]	7.02 ± 0.20	7.32 ± 0.11*	-	-
13 weeks	7.65 ± 0.07	7.73 ± 0.07[j]	7.81 ± 0.11[e]	-	-	-
Mean cell volume (fL)						
4 weeks (P=0.047N)	59.8 ± 0.2	58.8 ± 0.4	59.0 ± 0.5	59.2 ± 0.4	58.8 ± 0.2*	58.3 ± 0.3*[g]
8 weeks	63.8 ± 0.2	63.8 ± 0.3[f]	63.4 ± 0.2	63.4 ± 0.4	-	-
13 weeks (P=0.004N)	64.3 ± 0.2	63.8 ± 0.2*[j]	63.3 ± 0.3**[e]	-	-	-
Mean cell hemoglobin (pg)						
4 weeks	22.6 ± 0.1	22.3 ± 0.1	22.4 ± 0.1	22.4 ± 0.2	22.2 ± 0.1*	22.4 ± 0.1[g]
8 weeks	22.8 ± 0.1	22.6 ± 0.1[f]	22.7 ± 0.1	22.5 ± 0.2	-	-
13 weeks	23.0 ± 0.1	22.9 ± 0.1[j]	22.8 ± 0.1[e]	-	-	-
Mean cell hemoglobin concentration (g/dL)						
4 weeks	37.9 ± 0.1	37.9 ± 0.4	37.9 ± 0.3	37.9 ± 0.3	37.7 ± 0.2	38.4 ± 0.2[g]
8 weeks	35.5 ± 0.1	35.6 ± 0.3[f]	35.9 ± 0.1	35.5 ± 0.3	-	-
13 weeks	35.8 ± 0.2	36.0 ± 0.1[j]	36.0 ± 0.1[e]	-	-	-
Leukocytes ($10^3/\mu L$)						
4 weeks (P=0.044)	5.84 ± 0.68	5.40 ± 0.43	6.14 ± 0.36	6.00 ± 0.77	7.00 ± 0.72	7.23 ± 1.48[g]
8 weeks	4.80 ± 0.38	4.68 ± 0.27[f]	4.56 ± 0.34	4.72 ± 0.28	-	-
13 weeks	6.57 ± 0.47	5.80 ± 0.36[j]	6.96 ± 0.48[e]	-	-	-
Segmented neutrophils ($10^3/\mu L$)						
4 weeks	1.03 ± 0.16	1.01 ± 0.11	1.22 ± 0.28	1.02 ± 0.17	1.54 ± 0.18	1.22 ± 0.43[g]
8 weeks	0.79 ± 0.12	0.90 ± 0.05[f]	0.67 ± 0.13	0.99 ± 0.21	-	-
13 weeks	1.49 ± 0.14	1.12 ± 0.16[j]	1.31 ± 0.14[e]	-	-	-
Lymphocytes ($10^3/\mu L$)						
4 weeks	4.69 ± 0.67	4.33 ± 0.40	4.76 ± 0.20	4.81 ± 0.64	5.17 ± 0.63	5.68 ± 1.02[g]
8 weeks	3.87 ± 0.31	3.61 ± 0.27[f]	3.68 ± 0.23	3.45 ± 0.19	-	-
13 weeks	4.79 ± 0.35	4.52 ± 0.41[j]	5.49 ± 0.40[e]	-	-	-
Monocytes ($10^3/\mu L$)						
4 weeks (P=0.040)	0.09 ± 0.02	0.05 ± 0.02	0.09 ± 0.02	0.08 ± 0.03	0.20 ± 0.08	0.22 ± 0.04[g]
8 weeks	0.11 ± 0.03	0.14 ± 0.04[f]	0.13 ± 0.03	0.20 ± 0.04	-	-
13 weeks	0.21 ± 0.04	0.10 ± 0.03[j]	0.10 ± 0.04[e]	-	-	-

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Female (continued)						
Hematology (continued)						
Eosinophils ($10^3/\mu L$)						
4 weeks	0.03 ± 0.02	0.01 ± 0.01	0.07 ± 0.06	0.07 ± 0.04	0.09 ± 0.06	0.11 ± 0.05[g]
8 weeks	0.03 ± 0.02	0.03 ± 0.03[f]	0.06 ± 0.02	0.08 ± 0.04	–	–
13 weeks	0.07 ± 0.01	0.05 ± 0.01[j]	0.06 ± 0.02[e]	–	–	–
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
4 weeks (P<0.001)	16.4 ± 0.7	17.5 ± 0.8	19.3 ± 0.9*	20.8 ± 1.2**	21.3 ± 1.8*	26.4 ± 4.0**[g]
8 weeks (P<0.001)	16.3 ± 0.5	18.2 ± 0.6	19.2 ± 1.1*	22.1 ± 1.1**	–	–
13 weeks	16.2 ± 0.4	17.8 ± 0.6[j]	17.2 ± 0.6[j]	–	–	–
Creatinine (mg/dL)						
4 weeks	0.54 ± 0.02	0.50 ± 0.05	0.54 ± 0.05	0.48 ± 0.02	0.46 ± 0.02	0.47 ± 0.07[g]
8 weeks	0.60 ± 0.03	0.58 ± 0.04	0.62 ± 0.04	0.54 ± 0.02	–	–
13 weeks	0.63 ± 0.02	0.59 ± 0.03[j]	0.59 ± 0.03[j]	–	–	–
Sodium (mEq/L)						
4 weeks	150 ± 1[f]	150 ± 1	150 ± 3	144 ± 4	147 ± 1	149 ± 1[g]
8 weeks (P=0.002N)	150 ± 1	147 ± 0*	146 ± 1*[f]	146 ± 0**	–	–
13 weeks	147 ± 1	146 ± 1[j]	147 ± 1[j]	–	–	–
Potassium (mEq/L)						
4 weeks	6.6 ± 0.4[f]	6.4 ± 0.2	6.7 ± 0.3	6.7 ± 0.5	6.7 ± 0.3	7.2 ± 0.2[g]
8 weeks	6.1 ± 0.2	5.8 ± 0.1	5.8 ± 0.3[f]	6.1 ± 0.2	–	–
13 weeks (P<0.001)	5.4 ± 0.1	5.6 ± 0.1[j]	6.0 ± 0.1**[j]	–	–	–
Chloride (mEq/L)						
4 weeks	111 ± 1[f]	111 ± 1	110 ± 1	107 ± 3	109 ± 1	111 ± 1[g]
8 weeks (P=0.042N)	110 ± 0	109 ± 1	109 ± 1*[f]	109 ± 1*	–	–
13 weeks	108 ± 2	107 ± 0[j]	107 ± 0[j]	–	–	–
Calcium (mg/dL)						
4 weeks (P=0.023N)	10.5 ± 0.1	10.3 ± 0.1	10.4 ± 0.1	10.2 ± 0.1*	10.3 ± 0.1	10.2 ± 0.2[g]
8 weeks (P=0.047N)	11.0 ± 0.1	10.8 ± 0.2	10.6 ± 0.1	10.5 ± 0.2	–	–
13 weeks (P=0.015N)	11.2 ± 0.2	10.5 ± 0.2*[j]	10.5 ± 0.1*[j]	–	–	–
Phosphorus (mg/dL)						
4 weeks (P=0.047)	8.0 ± 0.5	8.0 ± 0.5	8.5 ± 0.4	8.1 ± 0.4	8.5 ± 0.3	9.4 ± 0.2[g]
8 weeks	7.0 ± 0.3	7.0 ± 0.4	6.7 ± 0.3	7.8 ± 0.4	–	–
13 weeks	6.9 ± 0.3	7.3 ± 0.3[j]	7.4 ± 0.3[j]	–	–	–
Total protein (g/dL)						
4 weeks	6.7 ± 0.1	6.6 ± 0.2	6.9 ± 0.1	6.4 ± 0.2	6.4 ± 0.1	6.6 ± 0.2[g]
8 weeks (P=0.003N)	7.2 ± 0.1	6.9 ± 0.1	6.7 ± 0.1**	6.7 ± 0.1**	–	–
13 weeks (P<0.001N)	6.9 ± 0.1	6.6 ± 0.1*[j]	6.5 ± 0.1**[j]	–	–	–
Albumin (g/dL)						
4 weeks	3.7 ± 0.0	3.7 ± 0.1	3.9 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.0[g]
8 weeks	3.7 ± 0.1	3.6 ± 0.0	3.6 ± 0.0	3.6 ± 0.0	–	–
13 weeks (P=0.003N)	3.7 ± 0.1	3.6 ± 0.1[j]	3.5 ± 0.0**[j]	–	–	–

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	30 mg/kg	60 mg/kg	90 mg/kg	120 mg/kg	150 mg/kg
Female (continued)						
Clinical Chemistry (continued)						
A/G ratio						
4 weeks	1.3 ± 0.0	1.3 ± 0.0	1.3 ± 0.0	1.4 ± 0.0	1.3 ± 0.0	1.3 ± 0.1[g]
8 weeks (P=0.024)	1.1 ± 0.0	1.1 ± 0.0	1.2 ± 0.0*	1.2 ± 0.0*	–	–
13 weeks	1.2 ± 0.0	1.2 ± 0.0[j]	1.2 ± 0.0[j]	–	–	–
Methemoglobin (%)						
4 weeks (P=0.006N)	8.35 ± 1.77	10.79 ± 2.63	9.35 ± 1.97	3.19 ± 1.91	3.26 ± 2.28	2.61 ± 2.27[g]
8 weeks	4.90 ± 1.39	2.23 ± 1.55[f]	3.63 ± 1.01	4.43 ± 1.39	–	–
13 weeks	4.50 ± 0.47	4.18 ± 0.40[j]	4.54 ± 0.84[e]	–	–	–
Alanine aminotransferase (IU/L)						
4 weeks (P<0.001)	34 ± 1	35 ± 1	38 ± 1*	38 ± 3	41 ± 2*	46 ± 2**[g]
8 weeks (P=0.014)	34 ± 1	35 ± 1	36 ± 3	43 ± 4	–	–
13 weeks	36 ± 1	34 ± 1[j]	39 ± 2[j]	–	–	–
Aspartate aminotransferase (IU/L)						
4 weeks (P=0.015)	99 ± 5	104 ± 6	105 ± 7	105 ± 9	142 ± 22	161 ± 36*[g]
8 weeks	80 ± 5	79 ± 4	89 ± 16	114 ± 18	–	–
13 weeks	78 ± 2	77 ± 3[j]	98 ± 13[j]	–	–	–
Lactate dehydrogenase (IU/L)						
4 weeks	688 ± 138	710 ± 116	759 ± 143	761 ± 143	786 ± 170	935 ± 145[g]
8 weeks	564 ± 87	542 ± 88	530 ± 65	640 ± 77	–	–
13 weeks	544 ± 50	588 ± 54[j]	621 ± 58[j]	–	–	–
Ornithine carbamyltransferase (IU/L)						
4 weeks	1 ± 0[g]	3 ± 1[f]	2 ± 0[g]	2 ± 0[c]	3 ± 1*[g]	–
13 weeks	6 ± 1[e]	3 ± 1[e]	3 ± 1[i]	–	–	–
Sorbitol dehydrogenase (IU/L)						
4 weeks	10 ± 1	10 ± 1	11 ± 1	10 ± 2	12 ± 1	14 ± 1[g]
8 weeks	14 ± 1	14 ± 1	17 ± 3	22 ± 5	–	–
13 weeks (P=0.018)	9 ± 1	11 ± 1[j]	12 ± 1*[j]	–	–	–
Cholinesterase (IU/mL)						
4 weeks (P<0.001N)	3.5 ± 0.1	3.0 ± 0.1*	2.9 ± 0.1*	2.3 ± 0.2**	1.9 ± 0.0**	1.7 ± 0.2**[g]
8 weeks (P<0.001N)	3.7 ± 0.2	2.7 ± 0.1**	2.7 ± 0.2**	2.2 ± 0.0**	–	–
13 weeks (P<0.001N)	3.5 ± 0.1	3.1 ± 0.1[j]	2.1 ± 0.1**[j]	–	–	–
Triiodothyronine (ng/dL)						
4 weeks	82 ± 7	85 ± 10	93 ± 7	82 ± 6	85 ± 6	97 ± 6[g]
8 weeks	83 ± 8	–	–	75 ± 7	–	–
Thyroxin (μg/dL)						
4 weeks (P=0.026)	4 ± 1	4 ± 0	5 ± 1	5 ± 1	6 ± 1	6 ± 0[g]
8 weeks	5 ± 1	–	–	6 ± 1	–	–

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

* 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. n=5 for weeks 4 and 8 and n=10 for week 13 except where noted.
[b] The entry by the week of sampling is the result of the trend test (Jonckheere, 1954) for significant trends only. Negative trends are indicated by N.
[c] n=2
[d] Insufficient data
[e] n=8
[f] n=4
[g] n=3
[h] n=7
[i] n=6
[j] n=9

TABLE G2
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Monochloroacetic Acid[a]

Analysis	Vehicle Control	15 mg/kg	30 mg/kg
Male			
n	7	7	7
Hematology			
Hematocrit (%)	44.2 ± 0.9	44.6 ± 0.6	44.8 ± 0.8
Hemoglobin (g/dL)	16.6 ± 0.3	16.8 ± 0.2	16.9 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.52 ± 0.09	8.41 ± 0.11	8.48 ± 0.14
Mean cell volume (fL)	52.0 ± 1.1	53.0 ± 0.8	53.0 ± 0.4
Mean cell hemoglobin (pg)	19.5 ± 0.4	20.1 ± 0.1	19.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.6 ± 0.2	37.8 ± 0.3	37.8 ± 0.2
Leukocytes ($10^3/\mu L$)	6.21 ± 0.55	6.44 ± 0.44	6.16 ± 0.32
Segmented neutrophils ($10^3/\mu L$)	1.81 ± 0.31	2.19 ± 0.42	1.97 ± 0.19
Lymphocytes ($10^3/\mu L$)	4.17 ± 0.31	4.06 ± 0.31	3.86 ± 0.30
Monocytes ($10^3/\mu L$)	0.16 ± 0.03	0.15 ± 0.02[b]	0.19 ± 0.03
Eosinophils ($10^3/\mu L$)	0.13 ± 0.02[b]	0.13 ± 0.02[b]	0.17 ± 0.02[b]
Nucleated erythrocytes ($10^3/\mu L$)	1.14 ± 0.55	0.43 ± 0.20	0.57 ± 0.43
Clinical Chemistry			
Total protein (g/dL)	6.8 ± 0.1	6.9 ± 0.2	6.8 ± 0.1
Albumin (g/dL)	3.6 ± 0.0	3.7 ± 0.1	3.7 ± 0.0
Alkaline phosphatase (IU/L)	64 ± 4	64 ± 4	68 ± 6
Alanine aminotransferase (IU/L)	70 ± 9	58 ± 5	63 ± 8
Creatine phosphokinase (U/L)	287 ± 30	251 ± 12	259 ± 11
Hydroxybutyrate dehydrogenase (IU/L)	298 ± 23	274 ± 16	282 ± 11
Lactate dehydrogenase (IU/L)	581 ± 48	525 ± 29	544 ± 23
Female			
n	7	7	7
Hematology			
Hematocrit (%)	43.9 ± 0.5[b]	43.5 ± 0.5	43.2 ± 0.5
Hemoglobin (g/dL)	16.6 ± 0.2[b]	16.4 ± 0.2	16.3 ± 0.2
Erythrocytes ($10^6/\mu L$)	7.64 ± 0.10[b]	7.64 ± 0.09	7.52 ± 0.18
Mean cell volume (fL)	57.3 ± 0.2[b]	57.0 ± 0.2	57.6 ± 0.8
Mean cell hemoglobin (pg)	21.7 ± 0.0[b]	21.5 ± 0.1	21.7 ± 0.4
Mean cell hemoglobin concentration (g/dL)	37.8 ± 0.2[b]	37.7 ± 0.2	37.6 ± 0.3
Leukocytes ($10^3/\mu L$)	3.98 ± 0.43[b]	4.03 ± 0.21	4.06 ± 0.32
Segmented neutrophils ($10^3/\mu L$)	1.30 ± 0.29[b]	1.33 ± 0.16	1.40 ± 0.28
Lymphocytes ($10^3/\mu L$)	2.53 ± 0.15[b]	2.50 ± 0.11	2.50 ± 0.14
Monocytes ($10^3/\mu L$)	0.10 ± 0.00[c]	0.14 ± 0.02[d]	0.10 ± 0.00[e]
Eosinophils ($10^3/\mu L$)	0.10 ± 0.00[e]	0.13 ± 0.03[e]	0.14 ± 0.02[d]
Nucleated erythrocytes ($10^3/\mu L$)	0.43 ± 0.30	0.43 ± 0.43	0.86 ± 0.34
Clinical Chemistry			
Total protein (g/dL)	7.1 ± 0.1	7.5 ± 0.2	7.2 ± 0.1
Albumin (g/dL)	4.0 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
Alkaline phosphatase (IU/L)	46 ± 4	44 ± 3	50 ± 2
Alanine aminotransferase (IU/L)	36 ± 3	38 ± 1	37 ± 2
Creatine phosphokinase (U/L)	190 ± 14	193 ± 14	219 ± 17
Hydroxybutyrate dehydrogenase (IU/L)	184 ± 12	186 ± 19	215 ± 21
Lactate dehydrogenase (IU/L)	335 ± 23	341 ± 35	407 ± 43

[a] Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test. MCV = mean cell volume.
[b] n=6
[c] n=3
[d] n=5
[e] n=4

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid[a]

Analysis	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Male[b]						
Hematology						
Hematocrit (%)						
4 weeks	40.5 ± 0.7	39.5 ± 0.8	36.1 ± 2.5[c]	41.1 ± 0.6	40.7 ± 0.7	40.4 ± 0.5
8 weeks	36.7 ± 1.6	37.9 ± 0.5	39.0 ± 0.2	37.7 ± 0.7	37.9 ± 0.8	37.2 ± 0.6[d]
13 weeks	38.4 ± 0.3[e]	36.0 ± 1.3	36.7 ± 1.1	38.3 ± 0.5	37.1 ± 0.3	–[f]
Hemoglobin (g/dL)						
4 weeks	15.7 ± 0.3	15.5 ± 0.3	14.4 ± 1.0[c]	15.8 ± 0.2	15.7 ± 0.3	15.8 ± 0.3
8 weeks	15.1 ± 0.7	15.5 ± 0.2	16.2 ± 0.2	15.6 ± 0.3	15.6 ± 0.3	15.3 ± 0.2[d]
13 weeks	16.3 ± 0.1[e]	15.5 ± 0.6	15.7 ± 0.5	16.5 ± 0.3	16.0 ± 0.2	–
Erythrocytes ($10^6/\mu L$)						
4 weeks	7.89 ± 0.09	7.68 ± 0.19	7.10 ± 0.48[c]	7.90 ± 0.18	7.99 ± 0.10	7.89 ± 0.08
8 weeks	7.45 ± 0.37	7.73 ± 0.08	7.97 ± 0.07	7.72 ± 0.10	7.72 ± 0.19	7.56 ± 0.14[d]
13 weeks	8.41 ± 0.07[e]	7.92 ± 0.31	7.98 ± 0.32	8.41 ± 0.13	8.16 ± 0.08	–
Mean cell volume (fL)						
4 weeks	51.2 ± 0.4	51.4 ± 0.2	51.8 ± 1.1	52.0 ± 0.8	51.0 ± 0.3	51.2 ± 0.4
8 weeks	49.4 ± 0.9	49.0 ± 0.0	49.0 ± 0.3	49.0 ± 0.3	49.0 ± 0.5	49.3 ± 0.3[d]
13 weeks	45.5 ± 0.2[e]	45.7 ± 0.5	46.3 ± 0.8	45.6 ± 0.2	45.5 ± 0.2	–
Mean cell hemoglobin (pg)						
4 weeks	19.9 ± 0.2	20.2 ± 0.2	20.7 ± 0.5	20.0 ± 0.3	19.7 ± 0.2	20.1 ± 0.3
8 weeks	20.3 ± 0.3	20.1 ± 0.1	20.4 ± 0.1	20.2 ± 0.1	20.2 ± 0.1	20.2 ± 0.2[d]
13 weeks	19.4 ± 0.1[e]	19.6 ± 0.1	19.8 ± 0.2	19.7 ± 0.1	19.6 ± 0.1	–
Mean cell hemoglobin concentration (g/dL)						
4 weeks	38.7 ± 0.2	39.4 ± 0.3	40.0 ± 0.2	38.4 ± 0.5	38.6 ± 0.3	39.2 ± 0.6
8 weeks	41.0 ± 0.2	40.9 ± 0.2	41.4 ± 0.3	41.4 ± 0.3	41.2 ± 0.4	41.2 ± 0.2[d]
13 weeks	42.6 ± 0.2[e]	43.2 ± 0.3	42.7 ± 0.3	43.2 ± 0.2	43.2 ± 0.2	–
Leukocytes ($10^3/\mu L$)						
4 weeks	1.70 ± 0.56	1.26 ± 0.35	2.28 ± 0.70[c]	1.42 ± 0.30	1.72 ± 0.40	1.22 ± 0.19
8 weeks (P=0.047)	3.32 ± 0.59	2.86 ± 0.48	3.38 ± 0.62	4.16 ± 0.68	4.28 ± 0.25	5.13 ± 1.79[d]
13 weeks	3.64 ± 0.64[e]	3.38 ± 0.70[g]	4.13 ± 0.97	3.47 ± 0.43	2.35 ± 0.38	–
Segmented neutrophils ($10^3/\mu L$)						
4 weeks	0.50 ± 0.20	0.36 ± 0.14	0.63 ± 0.30[c]	0.47 ± 0.12	0.33 ± 0.10	0.40 ± 0.16
8 weeks	0.68 ± 0.16	0.55 ± 0.04	0.60 ± 0.10	0.77 ± 0.17	0.78 ± 0.07	1.14 ± 0.54[d]
13 weeks (P=0.044N)	0.82 ± 0.17[e]	0.80 ± 0.16[g]	0.83 ± 0.19	0.64 ± 0.16	0.50 ± 0.09	–
Lymphocytes ($10^3/\mu L$)						
4 weeks	1.17 ± 0.38	0.88 ± 0.22	1.60 ± 0.51[c]	1.11 ± 0.25[c]	1.36 ± 0.29	0.81 ± 0.08
8 weeks	2.54 ± 0.44	2.26 ± 0.47	2.67 ± 0.50	3.21 ± 0.49	3.33 ± 0.23	3.85 ± 1.17[d]
13 weeks	2.78 ± 0.56[e]	2.47 ± 0.56[g]	3.20 ± 0.76	2.80 ± 0.38	1.81 ± 0.34	–
Monocytes ($10^3/\mu L$)						
4 weeks	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.02[c]	0.02 ± 0.01	0.03 ± 0.02	0.01 ± 0.00
8 weeks	0.10 ± 0.02	0.05 ± 0.02	0.11 ± 0.03	0.17 ± 0.05	0.17 ± 0.04	0.14 ± 0.10[d]
13 weeks	0.03 ± 0.01[e]	0.10 ± 0.03[g]	0.10 ± 0.05	0.02 ± 0.01	0.04 ± 0.02	–
Eosinophils ($10^3/\mu L$)						
4 weeks	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
13 weeks	0.01 ± 0.01[e]	0.02 ± 0.02[g]	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	–

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Male (continued)						
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
13 weeks	25.6 ± 3.6[c]	37.1 ± 5.0[c]	33.5 ± 4.7[c]	27.1 ± 3.4[h]	29.3 ± 2.5[i]	-
Total protein (g/dL)						
8 weeks	8.0 ± 0.6[c]	8.1 ± 0.4[d]	-	-	-	7.1 ± 0.5[d]
13 weeks	7.6 ± 0.5[h]	7.4 ± 0.3[h]	-	-	7.2 ± 0.5[h]	-
Albumin (g/dL)						
8 weeks	3.6 ± 0.1[c]	3.6 ± 0.0[d]	-	3.5 ± 0.1[h]	-	3.3 ± 0.2[d]
13 weeks	4.1 ± 0.1[c]	3.8 ± 0.3[d]	3.9 ± 0.2[h]	-	3.9 ± 0.1[i]	-
A/G ratio						
8 weeks	0.9 ± 0.1[c]	0.8 ± 0.1[d]	-	-	-	0.9 ± 0.0[d]
13 weeks	1.2 ± 0.2[h]	0.9 ± 0.0[h]	-	-	1.1 ± 0.1[h]	-
Methemoglobin (%)						
4 weeks	27.09 ± 3.12	27.34 ± 2.46	32.77 ± 1.46[d]	26.28 ± 3.82	29.02 ± 1.95	29.75 ± 2.23
8 weeks	6.68 ± 0.56	-	-	8.27 ± 1.31	-	6.60 ± 1.22[d]
13 weeks	10.25 ± 1.66[e]	-	-	7.88 ± 2.09	-	-
Alanine aminotransferase (IU/L)						
4 weeks	98 ± 36[c]	97 ± 29[h]	122 ± 34[c]	70 ± 15[d]	181 ± 32[h]	99 ± 28[c]
8 weeks	78 ± 29[d]	177 ± 62[d]	301 ± 14[*h]	184 ± 33[c]	200 ± 11[h]	151 ± 69[d]
13 weeks	150 ± 10[j]	223 ± 34	160 ± 28[e]	188 ± 39[g]	159 ± 24[g]	-
Aspartate aminotransferase (IU/L)						
13 weeks	256 ± 47[i]	230 ± 12[i]	236 ± 34[i]	200 ± 28[d]	335 ± 52[i]	-
Lactate dehydrogenase (IU/L)						
13 weeks	1,120 ± 168[d]	894 ± 234[h]	-	-	986 ± 225[c]	-
Sorbitol dehydrogenase (IU/L)						
4 weeks	97 ± 9	109 ± 9	94 ± 13[c]	105 ± 14	97 ± 11	115 ± 16
8 weeks	118 ± 11	113 ± 15	127 ± 15	102 ± 13	120 ± 21	109 ± 6[h]
Cholinesterase (IU/mL)						
8 weeks	7.8 ± 0.3	7.8 ± 0.1	7.6 ± 0.3	7.7 ± 0.3	7.7 ± 0.5	8.6 ± 0.3[d]
13 weeks	8.1 ± 0.4[e]	7.6 ± 0.5	7.7 ± 0.4[g]	8.4 ± 0.4	8.2 ± 0.3	-

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Female						
Hematology						
Hematocrit (%)						
4 weeks	40.0 ± 0.6	41.0 ± 0.9	40.4 ± 0.6	41.7 ± 0.7	39.8 ± 0.9	41.5 ± 0.5
8 weeks	38.5 ± 0.5	39.0 ± 0.6	38.9 ± 0.9	38.5 ± 0.7	39.5 ± 0.7	39.2 ± 0.9
13 weeks	39.4 ± 0.4	38.9 ± 0.5	38.8 ± 0.3	40.2 ± 0.3[g]	38.5 ± 0.4	38.7 ± 0.6[e]
Hemoglobin (g/dL)						
4 weeks	15.7 ± 0.3	15.9 ± 0.2	15.8 ± 0.4	16.2 ± 0.3	15.4 ± 0.3	15.9 ± 0.2
8 weeks	15.5 ± 0.2	15.9 ± 0.2	15.7 ± 0.3	15.6 ± 0.2	15.9 ± 0.3	16.0 ± 0.4
13 weeks	16.7 ± 0.2	16.5 ± 0.2	16.5 ± 0.2	17.0 ± 0.1[g]	16.5 ± 0.2	16.4 ± 0.2[e]
Erythrocytes ($10^6/\mu L$)						
4 weeks	7.62 ± 0.13	7.79 ± 0.14	7.77 ± 0.16	7.92 ± 0.09	7.67 ± 0.17	7.88 ± 0.12
8 weeks	7.65 ± 0.09	7.80 ± 0.09	7.75 ± 0.17	7.57 ± 0.14	7.84 ± 0.12	7.87 ± 0.11
13 weeks	8.47 ± 0.06	8.38 ± 0.08	8.35 ± 0.08	8.62 ± 0.05[g]	8.29 ± 0.08	8.33 ± 0.10[e]
Mean cell volume (fL)						
4 weeks	52.4 ± 0.2	52.6 ± 0.4	51.8 ± 0.4	52.8 ± 0.4	52.2 ± 0.4	52.6 ± 0.5
8 weeks	50.2 ± 0.2	49.8 ± 0.2	50.0 ± 0.5	50.8 ± 0.4	50.6 ± 0.4	49.8 ± 0.5
13 weeks	46.5 ± 0.3	46.4 ± 0.2	46.4 ± 0.3	46.8 ± 0.2[g]	46.5 ± 0.2	46.4 ± 0.3[e]
Mean cell hemoglobin (pg)						
4 weeks	20.5 ± 0.1	20.4 ± 0.1	20.3 ± 0.2	20.5 ± 0.3	20.1 ± 0.3	20.2 ± 0.2
8 weeks	20.3 ± 0.1	20.4 ± 0.1	20.3 ± 0.1	20.5 ± 0.1	20.3 ± 0.1	20.3 ± 0.2
13 weeks	19.8 ± 0.1	19.7 ± 0.1	19.8 ± 0.1	19.8 ± 0.1[g]	19.9 ± 0.1	19.7 ± 0.1[e]
Mean cell hemoglobin concentration (g/dL)						
4 weeks	39.1 ± 0.3	38.8 ± 0.5	39.1 ± 0.5	38.9 ± 0.4	38.8 ± 0.4	38.4 ± 0.4
8 weeks	40.4 ± 0.1	40.8 ± 0.2	40.4 ± 0.1	40.5 ± 0.3	40.3 ± 0.3	40.8 ± 0.2
13 weeks	42.5 ± 0.3	42.5 ± 0.2	42.6 ± 0.2	42.3 ± 0.2[g]	43.2 ± 0.4	42.5 ± 0.3[e]
Leukocytes ($10^3/\mu L$)						
4 weeks	1.46 ± 0.32	1.92 ± 0.34	1.62 ± 0.51	1.58 ± 0.36	1.72 ± 0.38	1.76 ± 0.27
8 weeks	3.26 ± 0.37	2.74 ± 0.46	3.12 ± 0.20	2.72 ± 0.40	3.76 ± 0.40	3.32 ± 0.23
13 weeks	3.61 ± 0.39	3.30 ± 0.53	3.19 ± 0.19	3.60 ± 0.35[g]	3.27 ± 0.61	5.09 ± 0.50[e]
Segmented neutrophils ($10^3/\mu L$)						
4 weeks	0.38 ± 0.10	0.44 ± 0.12	0.46 ± 0.14	0.31 ± 0.09	0.55 ± 0.12	0.41 ± 0.13
8 weeks (P=0.022N)	0.84 ± 0.11	0.70 ± 0.12	0.56 ± 0.05	0.53 ± 0.12	0.67 ± 0.09[c]	0.46 ± 0.07[e]
13 weeks	0.69 ± 0.11	0.64 ± 0.08	0.67 ± 0.09	0.64 ± 0.08[g]	0.68 ± 0.13	0.92 ± 0.11[e]
Lymphocytes ($10^3/\mu L$)						
4 weeks	1.04 ± 0.25	1.45 ± 0.26	1.15 ± 0.39	1.24 ± 0.27	1.16 ± 0.27	1.33 ± 0.28
8 weeks	2.28 ± 0.37	1.98 ± 0.35	2.44 ± 0.20	2.09 ± 0.28	2.92 ± 0.42	2.73 ± 0.16
13 weeks (P=0.024)	2.35 ± 0.34	2.55 ± 0.44	2.44 ± 0.17	2.86 ± 0.34[g]	2.52 ± 0.48	4.02 ± 0.39[e]
Monocytes ($10^3/\mu L$)						
4 weeks	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
8 weeks	0.14 ± 0.02	0.06 ± 0.01	0.10 ± 0.02	0.10 ± 0.03	0.08 ± 0.03	0.12 ± 0.01
13 weeks	0.07 ± 0.03	0.07 ± 0.02	0.06 ± 0.01	0.06 ± 0.02[g]	0.06 ± 0.02	0.13 ± 0.02[e]
Eosinophils ($10^3/\mu L$)						
4 weeks	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
13 weeks	0.02 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.05 ± 0.03[g]	0.00 ± 0.00	0.02 ± 0.01[e]

TABLE G3
Hematology and Clinical Chemistry Data for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid (continued)

Analysis	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Female (continued)						
Clinical Chemistry						
Blood urea nitrogen (mg/dL)						
13 weeks	20.4 ± 2.7[d]	23.5 ± 3.0[j]	22.6 ± 2.2[c]	20.1 ± 1.6[d]	25.3 ± 1.3[j]	15.8 ± 0.9[h]
Albumin (g/dL)						
13 weeks	4.6 ± 0.2[d]	4.3 ± 0.1[c]	4.4 ± 0.2[c]	4.3 ± 0.1[h]	4.5 ± 0.1[c]	4.3 ± 0.3[h]
Methemoglobin (%)						
4 weeks	31.06 ± 1.72	29.91 ± 2.58	27.99 ± 3.25	28.67 ± 1.11	35.34 ± 3.32	29.55 ± 2.39
8 weeks	8.04 ± 1.81	-	-	6.45 ± 1.99	-	4.49 ± 1.27
13 weeks	8.04 ± 1.32	-	-	8.49 ± 1.56[g]	-	10.25 ± 2.40[e]
Alanine aminotransferase (IU/L)						
4 weeks (P=0.036N)	154 ± 58[c]	219 ± 57[c]	130 ± 38[c]	106 ± 16[c]	95 ± 15[d]	84 ± 28[c]
8 weeks	92 ± 35[h]	128 ± 23[c]	91 ± 22[c]	218 ± 46[h]	127 ± 43[h]	120 ± 27[d]
13 weeks	100 ± 14[g]	99 ± 13[g]	115 ± 12	114 ± 19[g]	113 ± 20[e]	152 ± 40[j]
Aspartate aminotransferase (IU/L)						
13 weeks	202 ± 33[c]	176 ± 13[k]	232 ± 33[j]	199 ± 19[c]	214 ± 24[k]	182 ± 2[h]
Lactate dehydrogenase (IU/L)						
13 weeks	603 ± 81[h]	778 ± 117[d]	683 ± 179[d]	-	-	-
Sorbitol dehydrogenase (IU/L)						
4 weeks	82 ± 5	81 ± 6	84 ± 9	72 ± 9	71 ± 9	72 ± 6
8 weeks	88 ± 7[c]	84 ± 7	81 ± 10	85 ± 7	93 ± 19	88 ± 4
Cholinesterase (IU/mL)						
8 weeks (P=0.005N)	13.0 ± 1.0[c]	11.1 ± 0.4	11.3 ± 0.5	11.4 ± 0.4	10.9 ± 0.4*	10.3 ± 0.5**
13 weeks (P=0.003N)	12.6 ± 0.5	11.3 ± 0.4	11.8 ± 0.4	11.5 ± 0.4[g]	11.1 ± 0.3*	10.3 ± 0.5**[e]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. n=5 for weeks 4 and 8 and n=10 for week 13 except where noted.
[b] The entry by the week of sampling is the result of the trend test (Jonckheere, 1954) for significant trends only. Negative trends are indicated by N.
[c] n=4
[d] n=3
[e] n=8
[f] Insufficient data
[g] n=9
[h] n=2
[i] n=5
[j] n=6
[k] n=7

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF MONOCHLOROACETIC ACID

Monochloroacetic acid was obtained from American Hoechst in one lot (lot no. C035826, batch no. 01). This lot was used throughout the 16-day, 13-week, and 2-year studies. Purity, identity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI), Kansas City, MO, and confirmed by the study laboratory. Reports of analyses performed in support of the studies are on file at NIEHS.

The study chemical, a white solid, was identified as monochloroacetic acid by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The spectra were consistent with those expected for the structure of monochloroacetic acid and with the literature (*Sadtler Standard Spectra*) (Figures H1 and H2).

The purity of the lot was determined to be about 99% by Karl Fischer water analysis, elemental analysis, thin layer chromatography, gas chromatography, and potentiometric titration. Potentiometric titration was performed with aqueous 0.1 N sodium hydroxide. Elemental analysis for carbon, hydrogen, and chlorine was in agreement with the theoretical values for monochloroacetic acid. Thin layer chromatography (TLC) was performed in silica gel plates with two solvent systems:

1) mixed hexane : acetone : acetic acid (50:40:10) and
2) toluene : ethyl acetate : acetic acid (70:25:5).

Visualization was accomplished with short wavelength (254 nm) ultraviolet light and with a methyl red and bromothymol blue spray. A major spot was noted with both solvent systems. Gas chromatography (GC) was performed with two columns using flame ionization detection and N_2 carrier gas at 70 mL/minute:

1) 10% SP-1200/1% H_3PO_4 on 80/100 mesh Chromosorb W (AW), column temperature program of 50° C for 5 minutes, then 50° to 180° C at 10° C/minute and
2) 60/80 mesh Carbopak C/0.3% Carbowax 20 M/0.1% H_3PO_4, column temperature program of 50° C for 5 minutes and then 50° C to 175° C at 10° C/minute.

Three impurities, with combined areas of less than 0.4%, were detected by both systems.

Stability studies performed with a GC-FID method (column: 10% SP-1200 / 1% H_3PO_4 on 80/100 Chromosorb W (AW), 1.8 m × 4 mm ID; column temperature 160° C, carrier gas N_2 at 70 mL/minute) found that the bulk chemical was stable for at least 2 weeks at temperatures up to 60° C. The bulk chemical was stored at room temperature at the study laboratory throughout the study period. The stability of the bulk chemical was monitored periodically at the study laboratory during all phases of the studies by potentiometric titration of aqueous solutions with 0.1 N NaOH using a combination electrode and by gas chromatography using the same method as the analytical laboratory. No change in the study material was detected.

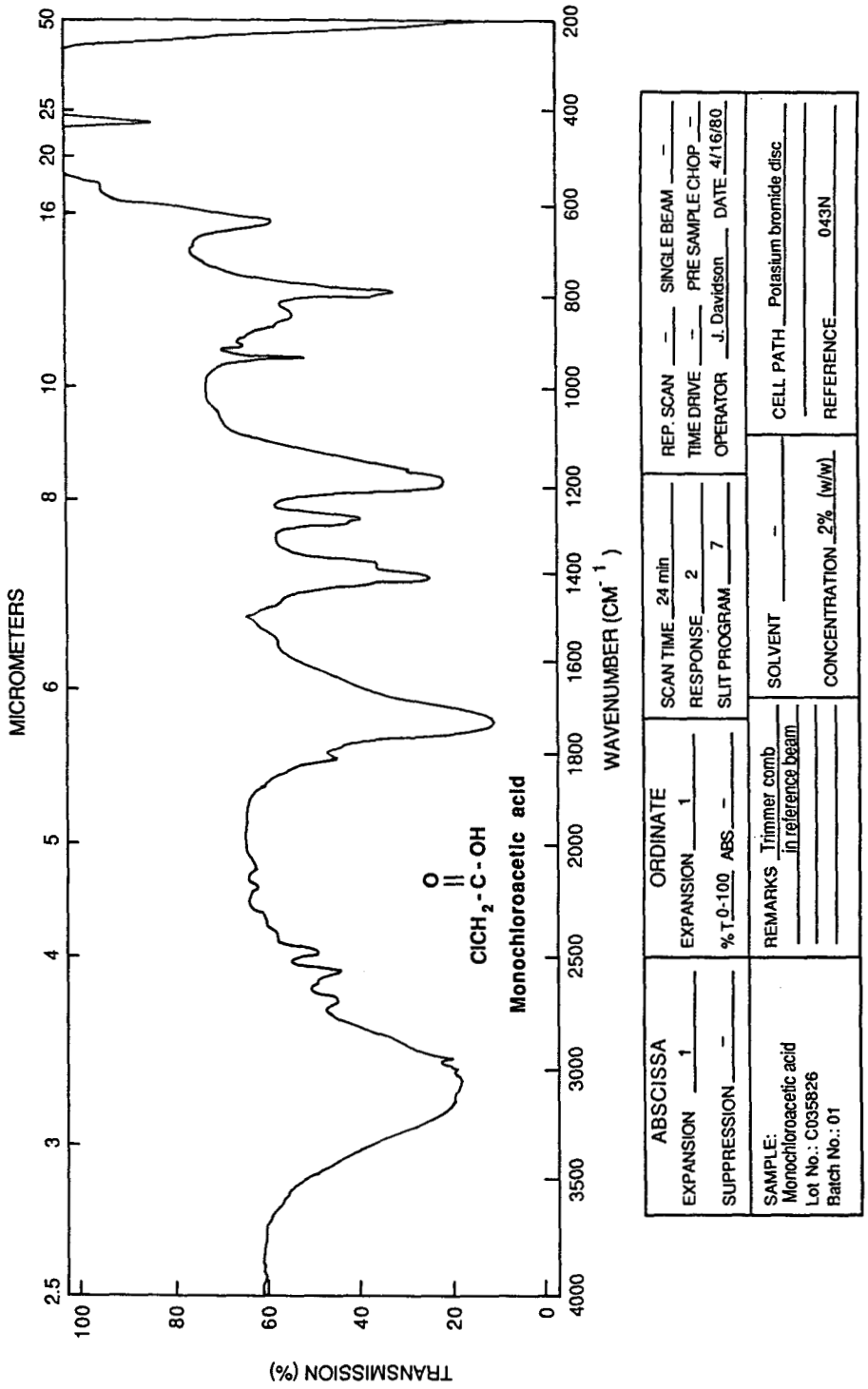

Figure H1
Infrared Absorption Spectrum of Monochloroacetic Acid

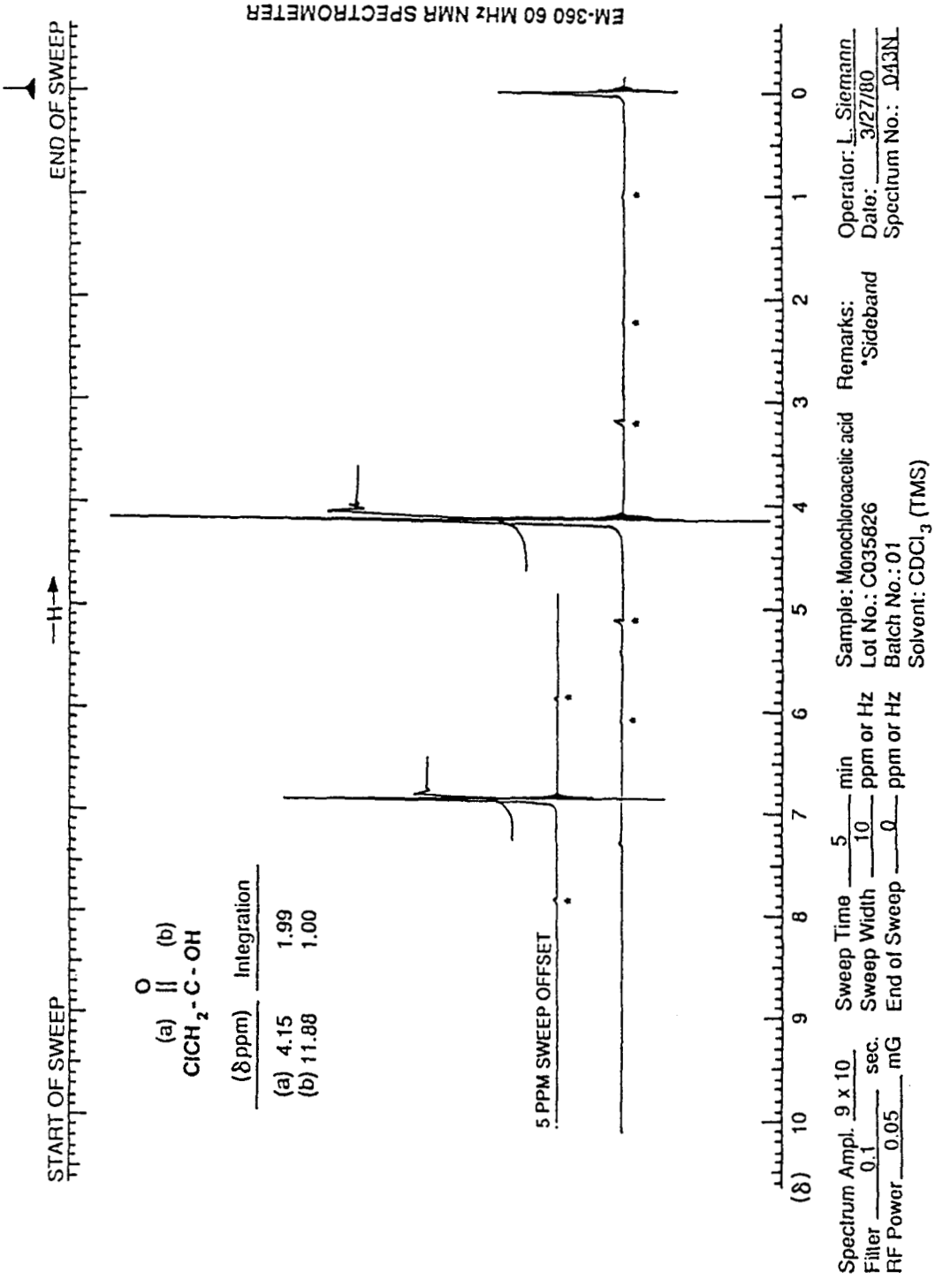

Figure H2
Nuclear Magnetic Resonance Spectrum of Monochloroacetic Acid

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The gavage route of administration was chosen for these studies because monochloroacetic acid was unstable in feed formulations, as determined by gas chromatographic analysis. The dose formulations were prepared by mixing appropriate amounts of monochloroacetic acid and deionized water to obtain the required concentrations. (Table H1). A 2-week stability study was conducted by the analytical chemistry laboratory prior to shipment of the test article to the study laboratory, and three 3-week stability analyses were performed on 3 mg/mL monochloroacetic acid/deionized water solutions at the study laboratory during the 2-year studies (dose formulations prepared on 28 June 1983, 27 February 1984, and 26 March 1984). The method involved dilution of the dose formulations with acetonitrile and injection into a GC-FID equipped with a 1.8 m × 2 mm ID column packed with 10% SP-1200/1% H_3PO_4 on 100/120 mesh Supelcoport; a column temperature of 135° C and a N_2 carrier flow rate of 30 mL/minute were used. The stability studies confirmed the stability of monochloroacetic acid solutions after storage for 3 weeks. The dose formulations were stored at room temperature in the dark for no longer than 2 weeks during the 16-day and 13-week studies and 3 weeks during the 2-year studies.

The study laboratory conducted periodic analyses of the monochloroacetic acid dose formulations using gas chromatography. Dose formulations were analyzed once during the 16-day studies, twice during the 13-week studies (Tables H2a and H2b), and at 8-week intervals during the 2-year studies (Tables H3a and H3b). During the subchronic studies, analysis of the aqueous formulations was by extraction with diethyl ether and subsequent flame ionization gas chromatography using nitrogen as the carrier gas, ether as diluent, and decanol as an internal standard. Dose formulations prepared on August 17, 1982, and November 9, 1982, for mice and on August 24, 1982, and November 2, 1982, for rats during the chronic studies were analyzed by ether extraction/gas chromatography using acetonitrile as diluent; for the remainder of the studies, test solutions were diluted directly with acetonitrile and then chromatographed using nitrogen as a carrier gas. During the 2-year studies, the dose formulations were within 10% of the target concentrations 93% (28/30) of the time for rats and 100% (28/28) of the time for mice (Tables H3a and H3b). Animal room samples from each dose level were analyzed every five to six months during the chronic studies and were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Tables H4a and H4b).

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of Monochloroacetic Acid

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Monochloroacetic acid was dissolved in deionized water at appropriate concentrations. Solutions and suspensions were prepared every 2 weeks.	Same as 16-day studies	Same as 16-day studies
Concentration		
Rats: 0, 0.75, 1.5, 3.0, 6.0, and 12.0 mg/mL Mice: 0, 1.5, 3.0, 6.0, 12.0, and 24.0 mg/mL for males; 0, 3.0, 6.0, 12.0, 24.0, and 48.0 mg/mL for females	Rats: 0, 6.0, 12.0, 18.0, 24.0, and 30.0 mg/mL Mice: 0, 2.5, 5.0, 10.0, 15.0, and 20.0 mg/mL	Rats: 0, 3.0, and 6.0 mg/mL Mice: 0, 5.0, and 10.0 mg/mL
Storage Conditions		
Room temperature in the dark	Room temperature in the dark	Room temperature in the dark
Maximum Storage Time		
2 weeks	2 weeks	3 weeks
Study Laboratory		
International Research and Development Corporation, Mattawan, MI	Same as 16-day studies	Same as 16-day studies
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 16-day studies	Same as 16-day studies

TABLE H2a
Results of Analysis of Dose Formulations for Rats in the 13-Week Gavage Studies of Monochloroacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined[a] Concentration (mg/mL)	Percent Difference from Target
11 August 1981	17 August 1981	0	–	–
		6.0	5.43	-9
		12.0	11.8	-2
		18.0	18.0	0
		24.0	22.1	-8
		30.0	30.1	0
22 September 1981	15 October 1981	0	–	–
		6.0	6.48	+8
		12.0	12.9	+8
		18.0	18.9	+5
		24.0	23.5	-2

[a] Results of duplicate analyses.

TABLE H2b
Results of Analysis of Dose Formulations for Mice in the 13-Week Gavage Studies of Monochloroacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined[a] Concentration (mg/mL)	Percent Difference from Target
18 August 1981	24 August 1981	0	–	–
		2.5	2.56	+2
		5.0	4.60	-8
		10.0	9.68	-3
		15.0	14.1	-6
		20.0	18.2	-9
29 September 1981	12 October 1981	0	–	–
		2.5	2.54	+2
		5.0	4.83	-3
		10.0	10.3	+3
		15.0	14.8	-1
		20.0	19.5	-3

[a] Results of duplicate analyses.

TABLE H3a
Results of Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Monochloroacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined[a] Concentration (mg/mL)	Percent Difference from Target
24 August 1982	31 August 1982	3.0	2.71	-10
		6.0	5.80	-3
24 August 1982	7 September 1982[b]	3.0	2.82	-6
		6.0	5.93	-1
2 November 1982	3 November 1982	3.0	2.92	-3
		6.0	6.06	+1
11 January 1983	24 January 1983	3.0	3.18	+6
		6.0	6.42	+7
8 February 1983	10 February 1983[b]	3.0	3.06	+2
		6.0	6.13	+2
8 March 1983	14 March 1983	3.0	3.08	+3
		6.0	6.09	+2
17 May 1983	25 May 1983	3.0	3.11	+4
		6.0	6.04	+1
14 June 1983	15 June 1983	3.0	3.17	+6
		6.0	6.03	+1
28 June 1983	28 June 1983	3.0	3.11	+3
		6.0	-[c]	-
26 July 1983	1 August 1983[b]	3.0	3.23	+8
		6.0	6.09	+1
23 August 1983	24 August 1983	3.0	3.26	+8
		6.0	6.07	+1
7 November 1983	8 November 1983	3.0	3.42	+14
		6.0	6.09	+2
9 November 1983	14 November 1983	3.0	3.37	+12
		6.0	-	-
14 November 1983	15 November 1983	3.0	2.89	-4
		6.0	-	-
3 January 1984	9 January 1984	3.0	3.15	+5
		6.0	6.00	0
3 January 1984	12 January 1984[b]	3.0	3.20	+7
		6.0	5.97	0
27 February 1984	1 March 1984	3.0	3.04	+1
		6.0	5.96	-1
26 March 1984	26 March 1984	3.0	3.00	0
		6.0	-	-
23 April 1984	23 April 1984	3.0	3.17	+5
		6.0	5.97	0
18 June 1984	18 June 1984	3.0	3.27	+9
		6.0	6.08	+1
18 June 1984	27 June 1984[b]	3.0	3.18	+6
		6.0	5.99	0
13 August 1984	13 August 1984	3.0	3.06	+2
		6.0	5.98	0

[a] Results of duplicate analyses for samples mixed on 8/24/82 and 11/02/82; triplicate analyses thereafter
[b] Animal room samples
[c] Not analyzed

TABLE H3b
Results of Analysis of Dose Formulations for Mice in the 2-Year Gavage Studies of Monochloroacetic Acid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined[a] Concentration (mg/mL)	Percent Difference from Target
17 August 1982	24 August 1982	5.0	4.61	-8
		10.0	9.73	-3
17 August 1982	1 September 1982[b]	5.0	4.85	-3
		10.0	10.63	+6
9 November 1982	12 November 1982	5.0	4.97	-1
		10.0	10.28	+3
18 January 1983	24 January 1983	5.0	4.94	-1
		10.0	10.69	+7
1 February 1983	3 February 1983[b]	5.0	4.87	-3
		10.0	10.24	+2
15 February 1983	16 February 1983	5.0	4.95	-1
		10.0	10.29	+3
10 May 1983	13 May 1983	5.0	5.24	+5
		10.0	10.67	+7
7 June 1983	8 June 1983	5.0	4.96	-1
		10.0	10.17	+2
19 July 1983	22 July 1983[b]	5.0	5.11	+2
		10.0	10.27	+3
16 August 1983	22 August 1983	5.0	5.03	+1
		10.0	10.09	+1
27 September 1983	27 September 1983	5.0	4.91	-2
		10.0	10.04	0
1 November 1983	8 November 1983	5.0	5.13	+2
		10.0	10.12	+2
27 December 1983	29 December 1983	5.0	5.04	+1
		10.0	10.16	+2
27 December 1983	5 January 1984[b]	5.0	5.05	+1
		10.0	10.22	+2
21 February 1984	24 February 1984	5.0	5.02	0
		10.0	10.26	+3
17 April 1984	20 April 1984	5.0	4.97	-1
		10.0	10.13	+1
12 June 1984	14 June 1984	5.0	5.12	+2
		10.0	10.13	+1
12 June 1984	21-22 June 1984[b]	5.0	4.94	-1
		10.0	10.08	+1
7 August 1984	8 August 1984	5.0	4.78	-4
		10.0	10.03	0

[a] Results of duplicate analyses for samples mixed on 8/17/82 and 11/09/82; triplicate analyses thereafter
[b] Animal room samples

TABLE H4a
Results of Referee Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Monochloroacetic Acid

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory	Referee Laboratory[b]
08/23/83	3	3.26[a]	3.02
02/27/84	6	5.96[b]	5.97

[a] Results of duplicate analyses
[b] Results of triplicate analyses

TABLE H4b
Results of Referee Analysis of Dose Formulations for Mice in the 2-Year Gavage Studies of Monochloroacetic Acid

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory	Referee Laboratory[a]
08/17/82	5	4.61[b]	5.06
02/15/83	10	10.29[a]	9.75
06/12/84	5	5.12[a]	5.01

[a] Results of triplicate analyses
[b] Results of duplicate analyses

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

TABLE I1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE I2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyroxidine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.13 ± 1.17	21.3–26.3	25
Crude fat (% by weight)	5.13 ± 0.59	3.3–6.3	25
Crude fiber (% by weight)	3.47 ± 0.53	2.8–5.6	25
Ash (% by weight)	6.63 ± 0.38	5.7–7.3	25
Amino Acids (% of total diet)			
Arginine	1.320 ± 0.072	1.310–1.390	5
Cystine	0.319 ± 0.088	0.218–0.400	5
Glycine	1.146 ± 0.063	1.060–1.210	5
Histidine	0.571 ± 0.026	0.531–0.603	5
Isoleucine	0.914 ± 0.030	0.881–0.944	5
Leucine	1.946 ± 0.056	1.850–1.990	5
Lysine	1.280 ± 0.067	1.200–1.370	5
Methionine	0.436 ± 0.165	0.306–0.699	5
Phenylalanine	0.938 ± 0.158	0.665–1.050	5
Threonine	0.855 ± 0.035	0.824–0.898	5
Tryptophan	0.277 ± 0.221	0.156–0.671	5
Tyrosine	0.618 ± 0.086	0.564–0.769	5
Valine	1.108 ± 0.043	1.050–1.170	5
Essential Fatty Acids (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	12,582 ± 4,612	4,100–24,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1–48.0	5
Thiamine (ppm)	17.56 ± 3.84	12.0–27.0	25
Riboflavin (ppm)	7.60 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.80 ± 31.68	65.0–150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0–34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19–0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6–38.0	5
Choline (ppm)	3,122 ± 416.8	2,400–3,430	5
Minerals			
Calcium (%)	1.28 ± 0.18	1.11–1.54	25
Phosphorus (%)	0.97 ± 0.06	0.87–1.10	25
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	0.304 ± 0.064	0.268–0.420	5
Iron (ppm)	410.3 ± 94.04	262.0–523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.090–15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52–3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44–2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.15	0.17–0.77	25
Cadmium (ppm)	<0.10	–	25
Lead (ppm)	0.74 ± 0.62	0.33–3.37	25
Mercury (ppm)	<0.05	–	25
Selenium (ppm)	0.32 ± 0.07	0.13–0.42	25
Aflatoxins (ppb)	<5.0	–	25
Nitrate nitrogen (ppm)	9.20 ± 4.64	0.10–22.0	25
Nitrite nitrogen (ppm)	1.37 ± 1.69	0.10–7.20	25
BHA (ppm)[b]	4.08 ± 4.76	2.00–17.0	25
BHT (ppm)[b]	2.80 ± 2.57	1.00–12.0	25
Aerobic plate count (CFU/g)[c]	46,112 ± 34,525	6,600–130,000	25
Coliform (MPN/g)[d,e]	49.20 ± 125	3.00–460	25
Coliform (MPN/g)[f]	13.43 ± 16.43	3.00–43.00	23
E. coli (MPN/g)	3.00	–	25
Total nitrosamines (ppb)[g]	5.67 ± 5.81	1.80–30.90	25
N-Nitrosodimethylamine (ppb)[g]	4.61 ± 5.81	0.80–30.00	25
N-Nitrosopyrrolidine (ppb)[g]	1.07 ± 0.26	0.81–1.70	25
Pesticides (ppm)			
α-BHC[h]	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion[i]	0.12 ± 0.09	0.05–0.45	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Source of contamination: soy oil and fish meal
[c] CFU = colony forming unit
[d] MPN = most probable number
[e] Mean, standard deviation, and range include the large value of 460 MPN obtained in the batches milled September 23, 1982 and September 20, 1983.
[f] Mean, standard deviation, and range exclude the value given in [e].
[g] All values were corrected for percent recovery.
[h] BHC = hexachlorocyclohexane or benzene hexachloride
[i] Fifteen lots contained more than 0.05 ppm.

APPENDIX J
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 are untreated, and 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.

Upon arrival, 5 male and 5 female rats and 5 male and 5 female mice were sacrificed for the evaluation of the health status of the animals. Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups to serve as sentinel animals. Similarly, 15 $B6C3F_1$ mice of each sex were designated as sentinel animals. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

RATS

Test	Time of Analysis
ELISA	
RCV/SDA (sialodacryoadenitis virus)	6, 12, 18, and 24 months
Mycoplasma pulmonis	24 months
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
KRV (Kilham rat virus)	6, 12, 18, and 24 months
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
Sendai virus	6, 12, 18, and 24 months

MICE

Test	Time of Analysis
Complement Fixation	
MHV (mouse hepatitis virus)	6 months
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
M. Ad. (mouse adenoma virus)	12, 18, and 24 months
ELISA	
MHV (mouse hepatitis virus)	12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	24 months
Mycoplasma pulmonis	24 months
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
Reovirus type 3	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months
Polyoma virus	6, 12, 18, and 24 months
Sendai virus	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Ectromelia virus	6, 12, 18, and 24 months

RESULTS

The serology results for sentinel animals are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of Monochloroacetic Acid

	Interval (months)	Number of Animals	Positive Serologic Reaction for
Rats			
	6	0/10	-
	12	10/10	RCV/SDA
		1/10	Sendai
	18	10/10	RCV/SDA
		5/10	PVM
	24	9/10	PVM
		8/10	RCV/SDA
		1/10	Sendai
Mice			
	6	1/10	MHV
	12	7/10	MHV
	18	10/10	MHV
	24	10/10	MHV
		2/10	*M. pulmonis*[a]

[a] Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX K
ACONITASE INHIBITION STUDIES IN LIVER AND HEART SAMPLES

ACONITASE INHIBITION STUDIES IN LIVER AND HEART SAMPLES

METHODS

Cardiomyopathy was observed in 13-week studies of male and female rats receiving monochloroacetic acid by gavage. Since a related compound, monofluoroacetic acid, produced toxicity through the inhibition of aconitase, a study was performed at the National Institute of Environmental Health Sciences comparing the degree of aconitase inhibition in liver and kidney from female rats receiving monochloroacetic acid or monofluoroacetic acid.

Nine female F344/N rats (weighing 150 to 170 g) were fasted 16 hours, divided into three groups and dosed by gavage. Three animals received deionized water (control vehicle); three animals received monofluoroacetic acid in deionized water (100 mg/kg, a dose equimolar to MCAA dose, positive control); and three animals received 150 mg/kg MCAA in deionized water. Animals 2, 5, and 8 were sacrificed around 45 minutes after dosing; animals 1, 4, 7 and 3, 6, 9 were sacrified around 1.5 hours after dosing. Livers and hearts were removed, placed in cold saline rinse, then homogenized in 0.25M sucrose and centrifuged at 9,000 x g for 20 minutes. The supernatants were removed and stored at -70° C for analysis.

The S9 mitochondrial protein levels were determined using the method of Lowry *et al.* The aconitase activities (or resulting inhibitions) were measured by the modified method of Sigma Chemical Co. Each assay cuvette contained 80.0 mM tris, pH 7.4, 1.3 mM manganous sulfate, 1.0 mM NADP, 0.4 units isocitric dehydrogenase, 1.5 mg S9 protein activated with 0.01 μmol ferrous ammonium sulfate and 0.5 μmol *l*-cysteine, pH 7.4, and various citric acid (the substrate) concentrations. The reaction was followed spectrophotometrically by measuring the increase in absorbance caused by the formation of NADPH at 340 nm.

Percent inhibitions have been calculated based on changes in optical densities. Preliminary data have not been converted to true rates of nmoles substrate per minute per mg protein; however, since all cuvettes had equal amounts of protein and NADP, data have been assumed to be comparable. (The aconitase activity assay has been verified by *in vitro* measurements.)

Substrate concentrations used were 0.1, 1, and 10 mM citric acid. Due to competitive inhibition mechanisms the best inhibition data were obtained using a 0.1 mM concentration.

RESULTS

A tabular summary of the aconitase activities is presented in Table K1.

TABLE K1
Summary of Aconitase Inhibition in *in vivo* Liver and Heart Samples at 0.1 mM Citrate Concentration

	Control		MFA			MCA		
	Animal No.	Aconitase Activity[a]	Animal No.	Aconitase Activity	% Inhibition[b]	Animal No.	Aconitase Activity	% Inhibition
Livers								
	1	6.2	2	1.8	71	3	7.0	none
	4	5.1	5	1.6	69	6	6.4	none
	7	6.3	8	2.4	62	9	7.1	none
Hearts								
	1	15.1	2	3.7	76	3	8.4	44
	4	13.0	5	2.5	81	6	8.7	33
	7	14.4	8	2.2	85	9	9.5	34

[a] nmoles substrate per minute per mg protein
[b] (Control minus MFA or MCA/control) × 100

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	1,3-Dichloropropane (Telone II®)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
387	Amphetamine Sulfate
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
393	Sodium Fluoride
395	Probenecid
399	Titanocene Dichloride

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DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
National Toxicology Program
Central Data Management
P.O. Box 12233, MD A0-01
Research Triangle Park, NC 27709

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