NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 408

TOXICOLOGY AND CARCINOGENESIS STUDIES OF MERCURIC CHLORIDE

(CAS NO. 7487-94-7)

IN F344 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.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF MERCURIC CHLORIDE

(CAS NO. 7487-94-7)

IN F344 RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

February 1993

NTP TR 408

NIH Publication No. 93-3139

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

C.J. Alden, Ph.D.
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
M.P. Dieter, 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.
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 Corporation

Conducted studies and evaluated tissues

B.M. Phillips, Ph.D., Principal Investigator
A.D. Boothe, D.V.M., Ph.D.
R.G. Geil, D.V.M., Ph.D.
D.C. Jessup, Ph.D.
D. Rajassekaran, D.V.M., M.V.Sc.
J.H. Thorstenson, Ph.D.
L.C. Uraih, D.V.M., M.S.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assessment

J.F. Hardisty, D.V.M., Principal Investigator
H.R. Brown, D.V.M., M.S.
B.F. Hamilton, D.V.M., Ph.D.

Integrated Laboratory Systems

Prepared pathology audits

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

NTP Pathology Working Group

Evaluated slides and prepared pathology report on rats (11 June 1990)

J.R. Leininger, D.V.M., Ph.D., Chair
Pathology Associates, Inc.
P.K. Hildebrandt, D.V.M., Study Pathologist
PATHCO
S. Imoto, D.V.M., Ph.D.
Shin Nippon Bio-Medical Laboratories
M.P. Jokinen, D.V.M.
National Toxicology Program
M. Lipsky, Ph.D.
University of Maryland
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

Evaluated slides and prepared pathology report on mice (11 June 1990)

M.A. Stedham, D.V.M., M.S., Chair
Pathology Associates, Inc.
E.T. Adams, D.V.M., Invited Observer
Michigan State University
G.A. Boorman, D.V.M., Ph.D.
National Toxicology Program
S. Imoto, D.V.M., Ph.D.
Shin Nippon Bio-Medical Laboratories
M.P. Jokinen, D.V.M.
National Toxicology Program
A.W. Macklin, D.V.M., Ph.D.
Burroughs Wellcome
H. Solleveld, D.V.M., Ph.D.
SmithKline Beecham Laboratories
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

Biotechnical Services, Inc.

Prepared Technical Report

L.G. Cockerham, Ph.D., Principal Investigator
G.F. Corley, D.V.M.
M.C. Hirrel, Ph.D.
K.D. Mencer, B.A.

CONTENTS

ABSTRACT

$HgCl_2$

MERCURIC CHLORIDE

CAS No. 7487-94-7

Chemical Formula: $HgCl_2$ Molecular Weight: 271.5

Synonyms: Abavit B, calochlor, corrosive sublimate, dichloromercury, mercuric bichloride, mercury chloride, mercury (II) chloride, mercury bichloride, mercury perchloride, sublimate, sulem, bichloride of mercury, corrosive mercury chloride, perchloride of mercury, mercury dichloride

Trade name: Fungchex

Mercuric chloride is an inorganic compound that has been used in agriculture as a fungicide, in medicine as a topical antiseptic and disinfectant, and in chemistry as an intermediate in the production of other mercury compounds. The widespread use of mercury has resulted in increased levels of mercury in rivers and lakes. Mercuric chloride was evaluated in toxicity and carcinogenicity studies because of its extensive use and its occurrence as an environmental pollutant, and because of the lack of adequate long-term rodent studies.

Toxicology and carcinogenesis studies were conducted by administering mercuric chloride (greater than 99% pure) in deionized water by gavage to groups of F344 rats or $B6C3F_1$ mice for 16 days, 6 months, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537), in mouse lymphoma L5178Y cells, in Chinese hamster ovary cells, and in *Drosophila melanogaster.*

16-Day Studies

Groups of five rats of each sex received 0, 1.25, 2.5, 5, 10, or 20 mg mercuric chloride/kg body weight and groups of five mice of each sex received 0, 5, 10, 20, 40, or 80 mg/kg in deionized water by gavage for 12 dose days. Two male rats in the 20 mg/kg group died in the first week, as did all male and four female mice from the 80 mg/kg group and one male mouse from the 40 mg/kg group. The final mean body weight of male rats receiving 20 mg/kg was 10% lower than that of the controls; the final mean body weight of 20 mg/kg females was 9% lower than that of the controls. Final mean body weights and body weight gains of dosed mice were similar to those of the controls. Absolute and relative kidney weights of male rats receiving 2.5 mg/kg or greater doses and of female rats administered 5 mg/kg or more were significantly greater than those of the controls. Absolute kidney weights of mice were significantly increased in all male dose groups and in the 40 mg/kg female dose group; relative kidney weights of dosed male and female mice were significantly greater than the controls. Analysis of kidney, liver, and brain tissues for mercury residues revealed that the highest mercury concentration was in the kidneys of rats and mice. Acute renal tubule nephropathy occurred in dosed rats and was slightly more severe in males than in females. Chemical-related lesions in mice included renal tubule necrosis, inflammation and necrosis of

the forestomach, and necrosis of the glandular stomach.

6-MONTH STUDIES

Groups of 10 rats of each sex received 0, 0.312, 0.625, 1.25, 2.5, or 5 mg mercuric chloride/kg body weight in deionized water by gavage for 26 weeks. Groups of 10 mice of each sex received 0, 1.25, 2.5, 5, 10, or 20 mg/kg in deionized water by gavage for 26 weeks (males) or 27 weeks (females). No deaths related to mercuric chloride administration occurred in rats or mice. Mean body weight gains of male rats that received 5 mg/kg and all female rat dose groups that received 0.625 mg/kg or greater were significantly lower than the controls. The final mean body weight and body weight gain of male mice in the 20 mg/kg group were significantly lower than those of the controls; final mean body weights and body weight gains of other dosed male mice and all dosed female mice were similar to those of the controls. Absolute and relative kidney weights of all dosed male rats and of female rats that received 0.625 mg/kg or greater were significantly greater than those of the controls. In male mice, absolute kidney weights in the three highest dose groups were significantly increased; no biologically significant differences in organ weights occurred in female mice. Analysis of kidney, liver, and brain tissues for mercury residues revealed the highest mercury concentration in the kidneys of rats and mice. The severity of chronic nephropathy increased with dose in male rats. Cytoplasmic vacuolation of renal tubule epithelial cells was observed in male mice in the 5, 10, and 20 mg/kg groups. No histopathologic changes in female mice were related to chemical exposure.

2-YEAR STUDIES

Groups of 60 rats of each sex received 0, 2.5, or 5 mg mercuric chloride/kg body weight and groups of 60 mice of each sex received 0, 5, or 10 mg/kg in deionized water by gavage 5 days per week for 2 years. The doses were based on decreased weight gains in rats receiving 10 and 20 mg/kg and the decreased weight in male mice receiving 40 mg/kg during the 16-day studies, and on the decreased weight gains and toxicity results seen in the 6-month studies. Increased absolute and relative kidney weights in rats and male mice in the 6-month studies and degenerative renal changes suggested that higher dose levels would result in inadequate survival rates for a 2-year study.

15-Month Interim Evaluations

Relative kidney weights were significantly increased in dosed rats and female mice. The severity of nephropathy was increased in male rats, but not in females. High-dose male and female rats had minimal to mild hyperplasia of the basal cell layer in the forestomach epithelium (diagnosed as acanthosis); this lesion was not found in control or low-dose rats. Male mice had an increased severity of vacuolation of the renal tubule epithelium; no chemical-related lesions occurred in the kidneys of females. The incidence of inflammation of the olfactory epithelium lining the nasal cavity increased in male and female high-dose mice.

Survival, Body Weights, and Clinical Signs

Survival of dosed male rats was lower than that of the controls (26/50, 10/50, 5/50); survival of dosed female rats was similar to that of the controls (35/50, 28/49, 30/50). Although more than 60% of the mice in each dose group survived to study end, survival rates of high-dose male mice and dosed female mice were lower than those of the controls (males: 36/50, 36/50, 31/50; females: 41/50, 35/50, 31/50). The final mean body weights of high-dose male and female rats were 15% and 14% lower than controls, respectively. The mean body weight of low-dose female rats was generally similar to controls throughout the 2-year study; the mean body weight of low-dose male rats was similar to that of the control through week 89. In mice, mean body weights of all male and female dose groups were similar to those of the controls throughout the studies.

Pathology Findings

Chronic nephropathy appeared to develop at an accelerated rate and led to decreased survival in both dosed male rat groups. Secondary effects of renal dysfunction in dosed male rats resulted in increased incidences of fibrous osteodystrophy of the bone, mineralization of various tissues, and parathyroid gland hyperplasia. Based on evaluations of single and step sections, the incidence of renal tubule hyperplasia was increased in high-dose male rats (control, 3/50; high-dose, 10/50), but the incidences of renal tubule adenoma in high-dose and control males were similar (4/50, 5/50). Renal tubule hyperplasia was also slightly increased in high-dose female rats (2/50,

5/50) and adenomas were seen in high-dose females, but not in controls (0/50, 2/50).

Incidences of forestomach hyperplasia in rats were markedly increased in dosed males (3/49, 16/50, 35/50) and high-dose females (5/50, 5/49, 20/50). Squamous cell papillomas of the forestomach were found in 3 low-dose and 12 high-dose males and in 2 high-dose females. No squamous cell carcinomas were found.

The incidence of thyroid follicular cell carcinoma was marginally increased in high-dose male rats (1/50, 2/50, 6/50). However, a corresponding increased incidence in follicular cell adenomas (1/50, 4/50, 0/50) or hyperplasias (2/50, 4/50, 2/50) in males did not occur, and the overall incidence of follicular cell neoplasms was not significantly increased (2/50, 6/50, 6/50).

The incidence of nasal mucosa inflammation in male and female rats was increased in the high-dose groups (male: 9/50, 8/47, 18/50; female: 0/49, 5/49, 15/50) and may have been related to chemical administration. The incidences of mammary gland fibroadenomas were significantly decreased in dosed female rats (15/50, 5/48, 2/50).

The incidence and severity of nephropathy were increased in dosed mice; secondary effects of renal dysfunction did not occur. Renal tubule hyperplasia was found in one control and two high-dose male mice. Two renal tubule adenomas and one renal tubule adenocarcinoma were seen in high-dose male mice. Additional step sections revealed focal hyperplasia in another control male; no additional renal tubule neoplasms were found in high-dose or control males. Proliferative lesions of the renal tubule epithelium were not found in female mice.

The incidence of metaplasia of the olfactory epithelium increased with dose in male and female mice. No other biologically significant lesions were found.

GENETIC TOXICOLOGY

Mercuric chloride was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with or without exogenous metabolic activation (S9). Induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* did not occur when mercuric chloride was administered in feed or by injection. However, positive results were obtained in mutagenicity tests with mammalian cells. In the absence of S9, mercuric chloride induced trifluorothymidine resistance in mouse L5178Y cells and chromosomal aberrations in Chinese hamster ovary cells. In the Chinese hamster ovary cell test for induction of sister chromatid exchanges, mercuric chloride produced a negative response without S9 and a weakly positive response in the presence of S9.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of mercuric chloride in male F344 rats based on the increased incidence of squamous cell papillomas of the forestomach. Marginally increased incidences of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in female F344 rats based on two squamous cell papillomas of the forestomach. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in male $B6C3F_1$ mice based on the occurrences of two renal tubule adenomas and one renal tubule adenocarcinoma. There was *no evidence of carcinogenic activity* of mercuric chloride in female $B6C3F_1$ mice receiving 5 or 10 mg/kg.

Nonneoplastic lesions associated with exposure to mercuric chloride included increased severity of nephropathy in male rats and male and female mice. There was an increased incidence of renal tubule hyperplasia in male rats. The incidence of forestomach hyperplasia was increased in dosed male and female rats. Increased incidences of nasal mucosa inflammation were associated with mercuric chloride administration in rats. Increased incidences of olfactory epithelial metaplasia in mice were also associated with mercuric chloride administration.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the peer review comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenicity and Genetic Toxicology Studies of Mercuric Chloride

Male F344 Rats	Female F344 Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 2.5, or 5.0 mg/kg in deionized water by gavage at a dose volume of 5 mL/kg	Same as male rats	0, 5, or 10 mg/kg in deionized water by gavage at a dose volume of 10 mL/kg	Same as male mice
Final body weights			
Dosed groups less than vehicle controls	Dosed groups less than vehicle controls	Dosed groups similar to vehicle controls	Dosed groups similar to vehicle controls
2-year survival rates			
26/50, 10/50, 5/50	35/50, 28/49, 30/50	36/50, 36/50, 31/50	41/50, 35/50, 31/50
Nonneoplastic effects			
Kidney: nephropathy (50/50, 46/50, 48/50); nephropathy average severity grades (2.66, 3.14, 3.32); renal tubule hyperplasia (3/50, 0/50, 10/50)	Forestomach: papillary hyperplasia (5/50, 5/49, 20/50)	Kidney: nephropathy (40/50, 45/50, 44/49); nephropathy average severity grades (1.08, 1.74, 2.51);	Kidney: nephropathy (21/49, 43/50, 42/50); nephropathy average severity grades (0.47, 1.02, 1.24)
Forestomach: papillary hyperplasia (3/49, 16/50, 35/50)	Nasal mucosa: inflammation (0/49, 5/49, 15/50)	Nasal mucosa: olfactory epithelial metaplasia (3/50, 8/50, 41/50)	Nasal mucosa: olfactory epithelial metaplasia (1/50, 20/50, 46/50)
Nasal mucosa: inflammation (9/50, 8/47, 18/50)			
Neoplastic effects			
Forestomach: squamous cell papilloma (0/50, 3/50, 12/50)	None	None	None
Uncertain findings			
Thyroid: follicular cell adenoma (1/50, 4/50, 0/50); follicular cell carcinoma (1/50, 2/50, 6/50)	Forestomach: squamous cell papilloma (0/50, 0/49, 2/50)	Kidney: renal tubule adenoma (0/50, 0/50, 2/49); renal tubule adenocarcinoma (0/50, 0/50, 1/49)	None
Levels of carcinogenic activity			
Some evidence	Equivocal evidence	Equivocal evidence	No evidence
Genetic toxicology			
Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA100, TA1535, TA1537, and TA98		
L5178Y mouse lymphoma cell gene mutation:	Positive for induction of trifluorothymidine resistance without S9		
Sister chromatid exchange Chinese hamster ovary cells *in vitro*:	Weakly positive with S9; negative without S9		
Chromosomal aberration Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with S9		
Sex-linked recessive lethal mutations *Drosophila melanogaster* germ cell mutation:	Negative administered by injection or in feed		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a 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 describes studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on mercuric chloride on July 10, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

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

Daniel S. Longnecker, M.D., Chair
Department of Pathology
Dartmouth Medical School
Lebanon, NH

Paul T. Bailey, Ph.D.
Toxicology Division
Mobil Oil Corporation
Princeton, NJ

Louis S. Beliczky, M.S., M.P.H., Principal Reviewer
Department of Industrial Hygiene
United Rubber Workers International Union
Akron, OH

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

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

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

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

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

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

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

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE

On July 10, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of mercuric chloride received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. G.A. Boorman, NIEHS, introduced the toxicology and carcinogenesis studies of mercuric chloride by discussing the uses and rationale for study. describing the experimental design including analysis of tissue and organ levels of mercury during a 6-month study, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in rats and mice. In summary, he thought the main concern with mercuric chloride should be toxicity, more so than carcinogenicity. The proposed conclusions were *some evidence of carcinogenic activity* in male F344 rats, *equivocal evidence of carcinogenic activity* in female F344 rats and male B6C3F$_1$ mice, and *no evidence of carcinogenic activity* in female B6C3F$_1$ mice.

Mr. Beliczky, a principal reviewer, agreed in principle with the conclusions. He thought that a statement regarding thyroid neoplasms in male rats should be deleted. He expressed concern that carcinogenicity data generated from the studies appeared to be compromised by the chemical toxicity, particularly in the kidney. Mr. Beliczky stated that if the severe toxicity of the chemical clearly limited the sensitivity of the study to detect carcinogenic effects, then the study design was limited or should have been modified after the 6-month study. Dr. Boorman agreed that in some cases, toxicity may have interfered with the ability to assess carcinogenicity.

Dr. Garman, the second principal reviewer, agreed with the conclusions. In view of the importance of the renal toxicity and the continuum which exists between hyperplasia, adenoma, and carcinoma, he suggested inclusion of a photomicrograph of a representative lesion of renal tubule hyperplasia (Plates 3 and 4).

Dr. Goodman, the third principal reviewer, agreed with the conclusions with the exception that he thought the second sentence should be qualified to read: "A marginally increased incidence of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure." Dr. Goodman commented on the statement in the genetic toxicology section that the induction of a high number of complex chromosomal aberrations implicated mercuric chloride as a major cause of damage, as opposed to cytotoxicity, which would be expected to produce mainly simple breaks. He considered this the sort of insight he would like to see more often, and asked that a reference or two be added.

Dr. Klaassen suggested that there be an expanded discussion of how the three forms of mercury — mercury vapor, organic mercury, and inorganic mercury salts — differ in toxicity. Dr. Boorman said a paragraph would be added. Dr. Carlson commented on the poor survival in dosed male rats and wondered about the adequacy of the study in male rats. Dr. J.K. Haseman, NIEHS, noted that survival to week 90 was about 60% in both dosed groups so a majority of animals survived long enough to be considered at risk for neoplasms. Further, since there was a positive effect for carcinogenicity, the low survival is less of a concern. Dr. Zeise thought the level of evidence in female rats should have been *some evidence* based on the two squamous cell papillomas in the high-dose group with supporting hyperplasia and similar increases in male rats. Dr. Boorman responded that based on only two neoplasms the staff did not think there was an unequivocal association with the chemical. Dr. McKnight argued that the three renal tubule neoplasms in high-dose male mice supported *some evidence*, particularly in view of zero incidence in concurrent controls and historical controls for water gavage studies. Dr. Boorman said the staff had considered this level; however, step sections of the kidneys failed to uncover any additional lesions in male or female mice, weakening the support for a chemical-associated effect.

Mr. Beliczky moved that the Technical Report on mercuric chloride be accepted with the revisions discussed, with the conclusions as written for male rats, *some evidence of carcinogenic activity*, for female rats and male mice, *equivocal evidence of carcinogenic activity*, and for female mice, *no evidence of*

carcinogenic activity, and with deletion of the second sentence: "An increased incidence of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure." The motion was tabled for lack of a second. Mr. Beliczky then moved that the conclusions be accepted as written including the second sentence. Dr. Garman seconded the motion. Dr. Goodman offered an amendment that the sentence have the word "marginally" added. Dr. Klaassen seconded the amendment, which was accepted by nine yes to one no votes (Dr. Zeise). Dr. Zeise offered an amendment that the conclusion for male mice be changed to *some evidence of carcinogenic activity*. Dr. McKnight seconded the amendment, which was defeated by eight no to two yes votes (Drs. McKnight, Zeise). Dr. Zeise offered an amendment that the conclusions for female rats be changed to *some evidence of carcinogenic activity*. The amendment was tabled for lack of a second. Mr. Beliczky's second motion to accept the conclusions as written with the second sentence amended to include the word "marginally" was then accepted by nine yes to one no votes (Dr. Zeise).

INTRODUCTION

$HgCl_2$

MERCURIC CHLORIDE

CAS No. 7487-94-7

Chemical Formula: $HgCl_2$ Molecular Weight: 271.5

Synonyms: Abavit B, calochlor, corrosive sublimate, dichloromercury, mercuric bichloride, mercury chloride, mercury (II) chloride, mercury bichloride, mercury perchloride, sublimate, sulem, bichloride of mercury, corrosive mercury chloride, perchloride of mercury, mercury dichloride

Trade name: Fungchex

MERCURY COMPOUND CHEMICAL PROPERTIES, PRODUCTION, AND EXPOSURE

Mercury is present in the atmosphere, soil, and water. Mercury concentrations in the atmosphere may reach levels of 50 ng/m^3 over industrialized and urban areas, 10 ng/L in ocean and coastal waters, 1,230 ng/L in rain and snow, and 50 ng/L in quality drinking water (WHO, 1976; Magos, 1987). Much of the mercury that has been released into the environment is found in the sediments of oceans, rivers, and lakes. The physicochemical states of mercury in the environment are complex and depend on a number of environmental factors, such as soil or sediment type, amount of organic matter and trace elements in the water, pH, sunlight, and the extent of adsorption to solid particles (Benes and Havlik, 1979).

As mercury is cycled through the biosphere, it is exchanged between environmental and biological systems. For example, some microbial activity converts inorganic mercury to organic methylmercury. In addition, some microbes, including certain *Pseudomonas* species, are capable of converting organic mercury to inorganic mercury, which may, under the appropriate conditions, form metallic mercury. Thus, biological factors, such as the presence and relative populations of microbial species, can affect environmental levels of mercury. However, not all aspects of the mercury cycling process are known.

Mercury is an environmental pollutant as well as a ubiquitous natural element. Man's use and release of mercury into the environment have caused twofold to fourfold increases in mercury concentrations in lakes and rivers (Andren and Nriagu, 1979). The sources of mercury pollution include the chloralkali, agriculture, health care, and coal burning industries, and research laboratories where mercury is found in electrical equipment, paints, measuring devices, and disinfectants (Berlin, 1986). Mercuric chloride is a widely used form of inorganic mercury. Annually, tons of mercuric chloride are released into the atmosphere by industrial processing and municipal waste incineration. Janicki *et al.* (1987) associated the use of mercury-containing fungicides with mercury levels in hair and the occurrence of leukemia in farmers. However, the study did not report sufficient epidemiological methodology, thus, further epidemiological studies are needed.

In the 1970's, world production of all types of mercury averaged between 6,000 and 10,000 metric

tons. During this time, the United States annually produced or imported approximately 2,000 metric tons.

The risk of mercury contamination in the environment has increased. Elevated levels of atmospheric contamination from the industrial release of organic and inorganic mercury compounds have increased the mercury content of the Greenland Icecap (IPCS, 1989) and of rivers and lakes (Andren and Nriagu, 1979). The largest source of atmospheric contamination by mercuric chloride is the incineration of municipal waste. The federal standard time-weighted average for organic mercury was set at 0.01 mg Hg/m^3 in 1986, while the National Institute for Occupational Safety and Health (NIOSH) maximum workplace exposure remains at 0.05 mg Hg/m^3. From a survey conducted from 1981 to 1983, NIOSH has estimated that 45,491 workers may have been exposed to mercuric chloride (NIOSH, 1990).

Toxicity of Mercury Compounds

Mercury may occur as three basic forms: elemental mercury, organic mercury, and inorganic mercury. Various salts or compounds are found in the organic and inorganic mercuries, and the toxicities of the mercury compounds vary widely. It is beyond the scope of this report to discuss the various mercury toxicities, so the discussion is generally limited to mercuric chloride and its toxicities. However, several excellent texts (Dreisbach, 1980; Gosselin *et al.*, 1984) may be consulted for comparative mercury toxicities.

Physical and Chemical Properties of Mercuric Chloride

Mercuric chloride is a colorless to white crystalline powder with a density of 5.4 g/cm^3, a melting point of 277° C, and a boiling point of 302° C. It volatilizes unchanged at about 300° C and is slightly volatile at room temperature. Mercuric chloride is corrosive and is soluble in water, ethanol, benzene, ether, glycerol, acetic acid, and several other organic solvents (*Merck Index*, 1983). Mercuric chloride is more dangerous than mercurous compounds because of its higher water solubility, 71.5 g/L at 25° C, and higher vapor pressure, 760 mm Hg at 304.0° C (Weast, 1982). In aqueous solution, mercuric chloride exists as chloride complexes which have strong tendencies to react with sulfhydryl groups, forming more stable sulfhydryl mercuric compounds.

Uses of Mercuric Chloride

Mercuric chloride is used in preservatives for wood and anatomical specimens, embalming solutions, disinfectants, photographic intensifiers, leather tanning, seed treatments, analytical reagents for organic syntheses, and the manufacture of other mercury-containing compounds. Pharmaceuticals containing mercuric chloride have also been used therapeutically as topical antiseptics and disinfectants (*Merck Index*, 1983).

Toxicity of Mercuric Chloride

Human Toxicity

Mercuric chloride is primarily a skin and mucous membrane irritant which is rapidly absorbed. Acute poisoning by ingestion or inhalation may cause severe nausea, vomiting, hematemesis, abdominal pain, diarrhea, melena, renal damage, and prostration. Ingestion of 1 to 2 g mercuric chloride may be fatal. Acute poisoning and death have also resulted from dermal applications of mercuric chloride solutions (*Merck Index*, 1983).

Animal Toxicity

Mercuric chloride is absorbed from the skin and the gastrointestinal tract, but only 2% is transported in the blood by the erythrocytes and plasma. Mercuric chloride does not readily cross the blood-brain barrier but will accumulate in the placenta (Berlin, 1986). The kidney is the primary site of mercury accumulation, followed by the liver. Thus, the kidney is a target organ for chronic mercuric chloride poisoning.

When aqueous mercuric chloride is administered to animals, mercuric chloride can react with proteins in the gastrointestinal tract via sulfhydryl groups, resulting in precipitation of the complexes and severe mucous membrane damage. These combined effects lead to very poor bioavailability of mercuric chloride. However, upon high oral intake, the permeability of the gastrointestinal tract may be altered by the corrosive action of mercuric chloride, and the absorption may be enhanced.

Berlin (1986) showed that only about 2% of orally administered mercuric chloride is absorbed in the gastrointestinal tract, and most of the absorbed mercuric chloride is accumulated in the kidneys.

Whole body elimination of mercury follows three distinct elimination phases with half-lives of approximately 3, 30, and 100 days in Wistar rats (Rothstein and Hayes, 1960). In short-term studies, the 30-day elimination phase would have the greatest impact on accumulation and toxicity of mercury. Therefore, in the NTP 16-day study, the concentration of mercury in the kidney would not have reached a steady state and would definitely be lower than concentrations reached after 6 months of exposure.

Exposure of animals to mercuric chloride primarily causes nephrotoxicity (Ganote *et al.*, 1974). The direct cytotoxic effect of mercuric chloride on the renal tubule has been studied extensively (Biber *et al.*, 1968; Barnes *et al.*, 1980). In rats, nephrotoxic doses of mercuric chloride produce selective alterations in the pars recta of the proximal tubule (Biber *et al.*, 1968). *p*-Aminohippuric acid is produced in the pars recta, and its secretion is very sensitive to mercuric chloride (Phillips *et al.*, 1977). The basic mechanism of mercuric chloride toxicity is not known, but mercury can combine with sulfhydryl groups and may inhibit most enzymes (Sin *et al.*, 1990). In an ultrastructural study of renal toxicity in rats, mercuric chloride at a dose of 1 mg/kg caused selective necrosis of the proximal tubules; however, the ultrastructural changes and oxygen consumption of renal tissue slices were not consistent with a primary mitochondrial defect. Mercuric chloride toxicity also has elicited immune responses in renal tissue. In rats, mercuric chloride exposure can injure the cells of the glomeruli, inducing an autoimmune reaction, or cause antibody production against the basement membrane of the glomeruli (Sapin *et al.*, 1977; Aten *et al.*, 1988).

CARCINOGENICITY OF MERCURIC CHLORIDE

A preliminary report suggested an association between mercury exposure and leukemia in farmers (Janicki *et al.*, 1987). Adequate epidemiological studies are still needed to assess the carcinogenic potential of mercuric chloride.

GENETIC TOXICITY

Early investigations of the mutagenicity of mercury compounds were reviewed by Ramel (1972) and Leonard *et al.* (1983). Although a large portion of the literature concerns studies with organic mercury compounds, test results are available on inorganic salts as well. Results from genetic toxicity studies using a variety of assays indicate that mercuric chloride is not mutagenic in bacteria or yeast, but that it may produce chromosomal damage and mitotic disruption (c-mitosis) in some plant and animal test systems.

Exposure to mercuric chloride did not result in growth inhibition due to DNA damage in the *Bacillus subtilis* rec-assay (Kada *et al.*, 1972; Nishioka, 1975; Matsui, 1980) and did not produce gene mutations in *Salmonella typhimurium* (Marzin and Phi, 1985; Zeiger *et al.*, 1987; Wong, 1988). Mitotic crossing-over was induced in *Saccharomyces cerevisiae*, although tests for gene conversion and reversion were negative (Fukunaga *et al.*, 1982). Positive results were obtained with mercuric chloride in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells (Oberly *et al.*, 1982; McGregor *et al.*, 1988).

Chromosomal damage induced by exposure to mercuric chloride has been reported by several laboratories; however, much of the data is difficult to interpret either because of data presentation or confounding factors within the experimental protocols. Regardless of the protocol used, results from these studies consistently demonstrate cytogenetic damage from mercuric chloride. The most numerous reports are those describing increases in DNA single strand breaks in mammalian cells *in vitro* (Robison *et al.*, 1982; Vasil'eva *et al.*, 1982; Zasukhina *et al.*, 1983; Cantoni and Costa, 1984; Christie *et al.*, 1984; Burkart and Ogorek, 1986; Cantoni *et al.*, 1986; Hamilton-Koch *et al.*, 1986) and *in vivo* (Cantoni *et al.*, 1982; Zasukhina *et al.*, 1983). Induction of sister chromatid exchanges by mercuric chloride has been reported *in vivo* in Chinese hamster bone marrow cells (Siebert, 1981), *in vitro* in Chinese hamster ovary K1 cells (Montaldi *et al.*, 1985), and in human lymphocytes (Morimoto *et al.*, 1982; Andersen, 1983). Increased frequencies of chromosomal aberrations occurred in liver cells of fetal mice following exposure of dams to mercuric chloride fumes on days 9 through 12 of gestation (Selypes *et al.*, 1983), and in human lymphocytes

exposed in culture to mercuric chloride (Verschaeve *et al.*, 1985).

Mercuric chloride was reported to be positive in a male rat dominant lethal assay, based on significant increases in resorptions and post-implantation deaths observed in untreated females mated to treated males (Vasil'eva *et al.*, 1982). In contrast, Suter (1975) did not consider results of a female mouse dominant lethal study as clear proof of a genetic effect induced by mercuric chloride, even though a slight increase in dead implants and a decrease in living embryos occurred when treated females were mated to untreated male mice, because maternal toxicity could not be ruled out.

Increased frequencies of aberrant mitoses were reported in embryonic tissue of the newt, *Pleurodeles waltl*, along with induction of micronuclei following growth in water containing mercuric chloride (Zoll *et al.*, 1988). Aberrant mitoses from mercuric chloride exposure also were found in *Allium cepa* root meristem cells (Dash *et al.*, 1988). Significant increases in inversions, translocations, breaks, and deletions occurred in the polytene chromosomes of fourth instar mosquito larvae (*Anopheles stephensi*) after 24 hours of exposure to mercuric chloride in water during the second instar stage (Sharma *et al.*, 1988). Verschaeve *et al.* (1985) have reported that inactivation of RNA polymerase I may cause the mitotic effects associated with exposure to mercury compounds; the mitoses may also be the result of mercury binding to sulfhydryl groups present in the spindle fiber proteins (Ramel, 1969; Jennette *et al.*, 1975; Verschaeve *et al.*, 1978).

STUDY RATIONALE

Mercuric chloride was nominated by the National Cancer Institute for toxicity and carcinogenicity studies because of its potential for widespread human exposure due to extensive use and large industrial production volume. Administration of mercuric chloride in water by gavage was selected as the route of exposure to ensure accurate and consistent exposure during the studies. Mercuric chloride was expected to exacerbate the naturally occurring renal disease of rodents, which increases water consumption; thus, drinking water administration was not chosen.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MERCURIC CHLORIDE

Mercuric chloride was obtained from the Fisher Scientific Company (Fairlawn, NJ) in one lot (lot number 792985), which was used throughout the 16-day, 6-month, and 2-year studies. Identity and purity analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO).

The study material, a white powder, was identified as mercuric chloride by elemental analyses performed by two independent analytical chemistry laboratories: Galbraith Laboratories, Incorporated (Knoxville, TN), and Huffman Laboratories, Incorporated (Wheat Ridge, CO). The purity was estimated to be greater than 99%. Water content was determined to be less than 0.1% using nuclear magnetic resonance (NMR) quantification. No inorganic impurities were found by X-ray emission analysis. No organic impurities were detected by ultraviolet/visible and NMR spectroscopies (Figure H1).

No bulk chemical stability studies were necessary because of the physical and chemical properties of mercuric chloride. Mercuric chloride has a melting point of approximately 277° C (*Merck Index*, 1983) and volatilizes without decomposition near 300° C. Because mercuric chloride is somewhat volatile at room temperature, the compound was stored protected from light in a Nalgene® container at room temperature.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations of the mercuric chloride solutions were prepared by mixing the appropriate amount of mercuric chloride in deionized water for the 16-day, 6-month, and 2-year studies. Stability studies were not conducted by the analytical laboratory because no appropriate analytical procedures were available to differentiate between covalently bonded mercuric chloride and the potential ionic species. However, the study laboratory analyzed dose formulations over a 3-week period to confirm that the total mercury concentrations did not change. Dose formulations were stored protected from light at room temperature for up to 3 weeks. For the 16-day studies, dose formulations were prepared once, with the exception of the 1.25 ppm rat formulation, which was prepared twice. For the 6-month and 2-year studies, dose formulations were prepared at least every 3 weeks (Table H1).

Dose formulations were routinely analyzed throughout the studies by ultraviolet spectroscopy to determine mercury concentration. In the 16-day studies, dose formulations were analyzed at study initiation (Table H2). In the 6-month studies, dose formulations were analyzed prior to initiation, at mid-point, and at termination (Table H3). In the 2-year studies, dose formulations were analyzed at least every 8 weeks for rats and mice (Tables H4 and H5). All dose formulations analyzed by the study laboratory were within 10% of the target concentrations. Results of the periodic referee analyses of the dose formulations by the analytical chemistry laboratory were in agreement with the results of analyses performed by the study laboratory (Table H6).

16-DAY STUDIES

Male and female F344 rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI). Animals were quarantined for 13 to 14 days before the studies began. The rats were 41 to 48 days old and the mice were 49 to 56 days old when the studies began.

Groups of five rats of each sex were administered 0, 1.25, 2.5, 5, 10, or 20 mg mercuric chloride/kg body weight in deionized water (dose volume 10 mL/kg) by gavage daily for 12 days, not including weekends, with 2 consecutive days of dosing before necropsy. Groups of five mice of each sex were administered 0, 5, 10, 20, 40, or 80 mg/kg in deionized water (dose volume 10 mL/kg) on the same schedule, with 3

consecutive dosing days before necropsy. Animals were housed five per cage. Water and feed were available *ad libitum*. Details of study design and maintenance are described in Table 1.

Animals were weighed at study initiation, on days 7 and 14, and at study termination. Animals were observed twice daily. Observations for signs of toxicity were made 0.5, 1, 2, 3, and 4 hours after dosing on the first 2 days of dosing then once daily, except on weekends, for the remainder of the studies. A complete necropsy was performed on all animals, including those dying before the end of the studies. Organ weights were obtained for the brain, heart, right kidney, liver, lung, and thymus of all animals surviving to study end. Brain, kidney, and liver tissue samples were collected from the control and highest dose groups and stored at −60° C for analysis of mercury residues according to the procedures described in Appendix I. Table 1 lists those tissues and organs examined microscopically.

6-Month Studies

Six-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to mercuric chloride, since 13-week studies were not considered adequate to determine the doses to be used in the 2-year studies. Male and female F344 rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Rats were observed for 15 days and mice were observed for 16 days before being assigned to treatment groups. Animals were distributed to weight classes and assigned to treatment groups by random numbers. The rats were 43 to 50 days old and the mice were 51 to 58 days old when dosing began.

Groups of 10 male and 10 female rats were administered 0, 0.312, 0.625, 1.25, 2.5, or 5 mg mercuric chloride/kg body weight in deionized water by gavage (dose volume 5 mL/kg), 5 days per week for 26 to 27 weeks. Similarly, 10 mice of each sex received doses of 0, 1.25, 2.5, 5, 10, or 20 mg/kg by gavage (dose volume 10 mL/kg) for 26 to 27 weeks. Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Details of study design are presented in Table 1.

Animals were observed twice daily. Once weekly, all animals were examined for toxic effects and were palpated for masses. Moribund animals were killed and necropsied. Individual animal weights were recorded on a weekly basis. Rats were also weighed prior to special study evaluation and at study termination.

There was also a concurrent study to determine tissue concentrations of mercury. Groups of 30 rats of each sex received 0, 0.312, 1.25, or 5 mg/kg mercuric chloride and 30 mice of each sex received 0, 1.25, 5, or 20 mg/kg by gavage 5 days per week for up to 27 weeks. Ten animals per dose group were selected for tissue residue analysis at months 2 and 4 and at study end. Kidney, liver, and blood samples were collected from all animals; brain samples were collected from control and high-dose animals. Brain, kidney, and liver tissue samples were stored at −60° C for analysis of mercury residues according to the procedures described in Appendix I. Histopathology was not performed on animals designated for mercury residue analysis.

After 6 months, all surviving animals not designated for mercury analysis were killed and necropsied. Organ weights were determined for the brain, heart, liver, lung, right kidney, and thymus of all animals, and the right testis of all males. Complete histopathologic examinations were performed on all rats in the control and 5 mg/kg dose groups, and on all mice in the control and the 20 mg/kg dose groups. Kidneys in males and females of both species from all dose groups were also examined.

The health of all animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K). Pinworms were observed in the 1.25 and 5 mg/kg female dose groups at week 5 and periodically throughout the study in both males and females in the higher dose groups until week 23. In sentinel animals, pinworms were observed only in females at week 5.

2-Year Studies

Study Design

Groups of 60 rats of each sex were administered 0, 2.5, or 5 mg mercuric chloride/kg body weight in deionized water by gavage (dose volume 5 mL/kg) 5 days per week for 103 to 104 weeks. Groups of 60 mice of each sex were given 0, 5, or 10 mg mercuric chloride/kg body weight in deionized water (dose volume 10 mL/kg) on the same schedule as rats.

Dosing was completed 8 to 10 days prior to study end. Ten rats and mice per dose group were designated for interim evaluations (necropsy, organ weights, histopathology, clinical chemistry, and urinalysis) after 15 months of chemical administration.

Source and Specification of Animals

The male and female F344 rats and B6C3F$_1$ mice used in the 2-year studies were obtained from Frederick Cancer Research Facility (Frederick, MD). Rats and mice were 29 days old when received by the study laboratory and were quarantined for 15 days. During quarantine, the animals were observed daily. To assess the health status of the animals, five rats and five mice per sex were killed and examined for disease and parasitic infection. The rats and mice were 44 days 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 K).

Animal Maintenance

Rats and female mice were housed five per cage. Male mice were housed five per cage until 18 October 1983; thereafter, they were individually housed. The cages were rotated within the racks and the racks within the room 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. Body weights were recorded weekly for the first 13 weeks and then every 4 weeks. During the last 3 months, body weights were determined once every 2 weeks. Clinical findings were recorded every 4 weeks. A necropsy was performed on all animals.

Blood and urine samples were collected from 10 randomly selected animals from each group for the 15-month evaluation. The animals were placed in metabolism chambers and urine samples were collected during an 18-hour fasting period. Blood samples were collected from the orbital sinus plexus at the end of the 18-hour period. The brain, right kidney, and liver of each 15-month interim evaluation animal were weighed at necropsy.

Complete histopathologic examinations were conducted on all control and high-dose animals at interim evaluation, animals that died or were killed moribund, and all animals killed at study termination following an 8- to 10-day withdrawal from treatment. Tissues for microscopic examination are listed in Table 1 and were preserved in phosphate-buffered neutral formalin, then embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Nonneoplastic lesions were rated using a four-step grading system of minimal, mild, moderate, and marked.

Pathology evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The laboratory animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated.

A quality assessment pathologist reviewed the kidney, thyroid gland, stomach, and forestomach of rats and the kidney and nasal passage of mice for accuracy and consistency of lesion diagnosis. In addition, all neoplastic diagnoses in tissues other than kidney were reviewed in all animals, and all diagnoses (neoplastic and nonneoplastic) were reviewed from a random 10% of the animals from each control and high-dose group. Since mercuric chloride exposure was associated with renal toxicity and since a low incidence of renal proliferative lesions was found in rats and male mice, an additional histopathologic review was undertaken on the kidneys from the controls and high-dose groups for rats and mice of each sex. All remaining formalin-fixed kidney tissue was embedded and step sectioned at 1 mm intervals, producing three to four tissue sections per kidney. A pathologist reviewed all the sections for proliferative lesions or neoplasms.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed the slides of tissues with potential treatment-related effects and of any other tissues for which there was disagreement in diagnoses between the laboratory and quality assessment pathologist. Representative histopathology slides of tissues with treatment-related lesions and examples of

disagreements in diagnosis between the laboratory and quality assessment pathologist were shown to the PWG. The PWG included the quality assessment pathologist and others experienced in rodent toxicologic pathology who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). The final pathology data represent a consensus of contractor pathologists and the PWG. A second PWG was held for the proliferative lesions identified in the additional renal step sections. The PWG chair reviewed all potential proliferative lesions that were recorded. The step section slides were then reviewed by the PWG members and the consensus diagnoses recorded. For the step sections, lesions that were not part of the spectrum of renal neoplasia (for example, the nephropathy found in aging rodents) were not recorded. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were separated 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 from other than natural causes. Animals dying from natural causes were not censored. Statistical analysis for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

The incidence of neoplasms 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 gland neoplasms) prior to tissue sampling for histopathology, or when lesions (e.g., mononuclear cell leukemia) could have occurred at multiple sites, the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms 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 neoplasms were discovered as the result of death from an unrelated cause and, thus, did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The control and dosed 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 neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals. Tests of significance include 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 neoplasm incidence, and reported P values are one sided. The procedures described above were also used to evaluate selected nonneoplastic lesions. For further discussion of these methods, see Haseman (1984).

Historical Control Data

Although the concurrent control group is 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 neoplasm incidence. Neoplasm incidences from the NTP historical control database are included for neoplasms appearing to show compound-related effects (Haseman *et al.*, 1984; 1985).

Analysis of Continuous Variables

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

QUALITY ASSURANCE METHODS

The 6-month and 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (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 Draft of this NTP Technical Report. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

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

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

Of the four *in vitro* tests evaluated by the NTP to date (mutagenicity in *Salmonella typhimurium*, mutagenicity in mouse lymphoma cells, chromosomal aberrations in cultured Chinese hamster ovary cells, or sister chromatid exchanges in cultured Chinese hamster ovary cells), a strong correlation exists between the potential electrophilicity of a chemical (structural alert to DNA reactivity), mutagenicity in *Salmonella typhimurium*, and carcinogenicity in rats and mice or at multiple tissue sites (Ashby and Tennant, 1991). The other *in vitro* tests do not correlate well with carcinogenicity in rodents (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). Mutagenicity in *Salmonella typhimurium* was the most predictive for rodent carcinogenicity (89% of the mutagens were carcinogens in rats and/or mice), whereas mutations in mouse lymphoma cells or chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells were less predictive of carcinogenicity; 63% of chemicals inducing mutations in mouse lymphoma cells, 73% of chemicals inducing chromosomal aberrations, and 64% of chemicals inducing sister chromatid exchanges were carcinogenic in rodents. Moreover, no battery of tests that included the *Salmonella typhimurium* test improved the predictability of the *Salmonella typhimurium* test alone. The predictivity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined. The reader is referred to the articles cited above for details regarding the correlation of structural alerts (or absence thereof), mutagenicity, and carcinogenicity results of 301 chemicals in the NTP database.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Mercuric Chloride

16-Day Studies	6-Month Studies	2-Year Studies
Study Laboratory		
International Research and Development Corporation (IRDC), Mattawan, MI	Same as 16-day studies	Same as 16-day studies
Strain and Species		
Rats: F344 Mice: $B6C3F_1$	Same as 16-day studies	Same as 16-day studies
Animal Source		
Charles River Breeding Laboratories, Inc., Portage, MI	Same as 16-day studies	Frederick Cancer Research Facility, Frederick, MD
Size of Study Groups		
5 males or 5 females per test group	10 males or 10 females per test group; special studies were conducted on 10 males or 10 females per test group at 2, 4, and 6 months	60 males or 60 females per test group; interim evaluations were conducted on 10 males or 10 females per test group at 15 months
Doses		
Rats: 0, 1.25, 2.5, 5, 10, or 20 mg/kg in deionized water administered by gavage in a dose volume of 10 mL/kg Mice: 0, 5, 10, 20, 40, or 80 mg/kg in deionized water administered by gavage in a dose volume of 10 mL/kg	Rats: 0, 0.312, 0.625, 1.25, 2.5, or 5 mg/kg in deionized water administered by gavage in a dose volume of 5 mL/kg Mice: 0, 1.25, 2.5, 5, 10, or 20 mg/kg in deionized water administered by gavage in a dose volume of 10 mL/kg	Rats: 0, 2.5, or 5 mg/kg in deionized water administered by gavage in a dose volume of 5 mL/kg Mice: 0, 5, or 10 mg/kg in deionized water administered by gavage in a dose volume of 10 mL/kg
Time Held Before Study		
Rats: 13 days Mice: 14 days	Rats: 15 days Mice: 16 days	Rats: 15 days Mice: 15 days
Age When Placed on Study		
Rats: 41-48 days Mice: 49-56 days	Rats: 43-50 days Mice: 51-58 days	Rats: 44 days Mice: 44 days
Date of First Dose		
Rats: 23 March 1981 Mice: 24 March 1981	Rats: 30 September 1981 Mice: 1 October 1981	Rats: 4 March 1983 Mice: 10 March 1983
Duration of Dosing		
12 of 16 days	5 days/week for 26 weeks (males); one additional dose in week 27 (females)	5 days/week for 103-104 weeks
Date of Last Dose		
Rats: 7 April 1981 Mice: 8 April 1981	Rats: 31 March 1982 Mice: 2 April 1982	Rats: 26 February 1985 Mice: 4 March 1985
Average Age at Necropsy		
Rats: 8-9 weeks Mice: 9-10 weeks	Rats: 32-33 weeks Mice: 33-34 weeks	110-111 weeks

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Mercuric Chloride (continued)

16-Day Studies	6-Month Studies	2-Year Studies
Necropsy Dates Rats: 8 April 1981 Mice: 10 April 1981	Rats: 5-9 April 1982; 62-day evaluation, 2 December 1981; 120-day evaluation, 28 January 1982 Mice: 5-9 April 1982; 62-day evaluation, 3 December 1981; 120-day evaluation, 29 January 1982	Rats: 1-6 March 1985; 15-month interim, 5 June 1984 Mice: 7-12 March 1985; 15-month interim, 7 June 1984
Method of Sacrifice CO_2	Same as 16-day studies	Same as 16-day studies
Method of Animal Distribution A computerized pseudo-random number generator selected the animals, which were computer-sorted by ascending body weight and sex. Blocks were arranged by weight and animals were assigned to treatment groups by random numbers.	Same as 16-day studies	Same as 16-day studies
Animals per Cage Rats: 5 Mice: 5	Same as 16-day studies	Rats: 5 Mice: 5; males housed individually beginning 18 October 1983
Method of Animal Identification Rats: ear tag Mice: toe clip	Same as 16-day studies	Same as 16-day studies
Diet NIH-07 Open Formula Rat and Mouse Ration, mash (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Water Source: Village of Mattawan, MI, and IRDC wells. Available *ad libitum* using an automatic water system (Edstrom Industries Inc., Waterford, WI)	Same as 16-day studies	Same as 16-day studies
Cages Polycarbonate with Edstrom grommets (Hazleton Systems, Inc., Aberdeen, MD), changed twice weekly	Same as 16-day studies	Same as 16-day studies
Bedding BetaChips®, heat-treated hardwood chips (Northeastern Products Corp., Warrensburg, NY), changed twice weekly	Same as 16-day studies	Same as 16-day studies, except male mice after 18 October 1983 changed once weekly
Cage Filters Reemay nonwoven polyester fiber filters (Snow Filtration, Cincinnati, OH), changed weekly	Reemay nonwoven polyester fiber filters (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 6-month studies

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Mercuric Chloride (continued)

16-Day Studies	6-Month Studies	2-Year Studies
Racks		
Stainless steel, rotated every 2 weeks	Same as 16-day studies	Same as 16-day studies
Animal Room Environment		
Average temperature: 23° C Relative humidity: 38%-39% Fluorescent light: 12 hours/day Room air flow: 6-12 changes/hour	Average temperature: 73° F Relative humidity: 39% Fluorescent light: 12 hours/day Room air flow: 6-12 changes/hour	Average temperature: 73° F Relative humidity: 49%-50% Fluorescent light: 12 hours/day Room air flow: 6-12 changes/hour
Type and Frequency of Observations		
Observed twice/day; body weight initially, once/week, and at study end; clinical observation daily except weekends	Observed twice/day; body weight initially, once/week, prior to special study evaluation, and at the end of the studies; clinical observation once/week. Animals were palpated weekly for masses.	Observed twice/day; body weights initially, once/week for 13 weeks, then once/4 weeks until 21 months, then once/2 weeks, at 15-month interim evaluation, and at the end of the studies; clinical observation once/4 weeks
Clinical Pathology		
None	Clinical pathology studies were conducted at 2, 4, and 6 months. ***Clinical chemistry:*** Rats- urea nitrogen, creatinine, sodium (2 and 4 months), potassium (2 and 4 months), chloride (2 and 4 months), calcium (2 and 4 months), phosphorus (2 and 4 months), total protein, albumin (2 and 4 months), A/G ratio (2 and 4 months), total bilirubin (2 and 4 months), acid phosphatase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase (2 and 4 months), lactate dehydrogenase, ornithine carbamoyltransferase (2 and 4 months), sorbitol dehydrogenase, serum cholinesterase, pH (2 and 4 months) Mice- urea nitrogen (2 and 4 months), calcium (4 months), total protein (males- 2 and 4 months; females- 4 months), albumin (2 and 4 months), A/G ratio (males- 2 and 4 months; females- 4 months), acid phosphatase, alkaline phosphatase, alanine aminotransferase (2 and 4 months), aspartate aminotransferase (2 and 4 months), lactate dehydrogenase (2 and 4 months), sorbitol dehydrogenase (2 and 4 months), pH (2 and 4 months)	Clinical pathology studies on rats and mice of both sexes for all dose groups were conducted at 15 months. ***Clinical chemistry:*** urea nitrogen, alkaline phosphatase, alanine aminotransferase, sorbitol dehydrogenase, and serum cholinesterase ***Urinalyses:*** urine nitrogen, urine creatinine, urine alkaline phosphatase, urine aspartate aminotransferase, urine lactate dehydrogenase, urine γ-glutamyltransferase, urine volume, and specific gravity
Necropsy		
Necropsy performed on all animals. Organs weighed at study termination were brain, heart, right kidney, liver, lung, and thymus.	Necropsy performed on all animals. Organs weighed were the same as in the 16-day studies plus the right testis.	Necropsy performed on all animals. Organs weighed at 15-month interim evaluations were brain, right kidney, and liver.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of Mercuric Chloride (continued)

16-Day Studies	6-Month Studies	2-Year Studies
Histopathology		
Complete histopathology on 20 mg/kg rats and 80 mg/kg mice including the following tissues: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, heart, kidney, large intestine, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, small intestine, spleen, stomach, testis (males), thymus, thyroid gland, trachea, urinary bladder, uterus (females), and gross lesions. The following organs were examined from rats in all dose groups: kidney, stomach, preputial gland (males), and clitoral gland (females). The following organs were examined from mice in all dose groups: kidney, stomach, and thymus.	Complete histopathologic examinations were performed on all control and high-dose rats and mice. Tissues examined were the same as in the 16-day studies and also included tissue masses and gallbladder (mice). The kidney was examined in all rats and mice.	Complete histopathologic examinations were conducted on all control and high-dose animals at interim evaluation, animals that died or were killed moribund, and all animals killed at study termination. Tissues examined were the same as the 16-day studies and included gallbladder (mice). Clitoral gland was examined only in female rats at study termination. The kidney from all low-dose mice was also examined at the 15-month interim evaluation.
Special Studies		
Mercury residue levels were determined for rats and mice of each sex for the following dose groups: rats, 0 and 20 mg/kg; mice, 0 and 40 mg/kg. Tissues analyzed were brain, kidney, and liver.	Mercury residue levels were determined at 2, 4, and 6 months from the following dose groups: rats, 0, 0.312, 1.25, and 5 mg/kg; mice, 0, 1.25, 5, and 20 mg/kg. Tissues analyzed were brain (control and high-dose groups), kidney, and liver.	None

RESULTS

RATS

16-Day Studies

Two males in the 20 mg/kg group died during the first week of mercuric chloride administration; all other rats survived to the end of the studies (Table 2). Final mean body weights of high-dose male and female rats were 10% and 9% lower than those of the controls, respectively. Body weight gains of male and female rats in the 10 and 20 mg/kg groups were significantly less than those of the controls.

Absolute and relative kidney weights increased in dosed rats and were significantly increased in males receiving 2.5 mg/kg mercuric chloride or greater and in females receiving 5 mg/kg or greater (Table F1). Significant decreases in absolute weights of heart, liver, lung, and thymus, and the significant increase in relative brain weight in females receiving 20 mg/kg were considered to be secondary to the reduced body weight. No other biologically significant organ weight changes were observed.

Kidney, liver, and brain tissues from the controls and 20 mg/kg groups were analyzed for mercury concentration. Tissue concentrations of mercury in the male and female vehicle control groups were less than 1 ppm in the kidney and less than 0.2 ppm in the liver and brain (Table I1). In the high-dose groups, mercury concentrations in kidney and liver tissues were 45.5 and 5.7 ppm for males and 43.4 and 4.4 ppm for females. Mercury concentrations of the brain were less than 0.5 ppm in the 20 mg/kg rats.

The administration of mercuric chloride at 5 mg/kg or greater for 16 days produced acute renal tubule necrosis (nephropathy) (Table 3). Renal tubule necrosis was slightly more severe in male rats than in female rats and occurred primarily within the outer stripe of the outer medulla.

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

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0.00	5/5	133 ± 6	187 ± 8	54 ± 3	–
1.25	5/5	134 ± 5	197 ± 7	63 ± 2	105
2.50	5/5	133 ± 7	194 ± 9	61 ± 3	104
5.00	5/5	134 ± 7	189 ± 8	55 ± 2	101
10.00	5/5	133 ± 4	176 ± 4	44 ± 3*	94
20.00	3/5[c]	135 ± 6	169 ± 9	38 ± 3**	90
Female					
0.00	5/5	106 ± 2	140 ± 4	34 ± 1	–
1.25	5/5	108 ± 2	139 ± 3	32 ± 2	99
2.50	5/5	108 ± 4	136 ± 4	29 ± 1	97
5.00	5/5	108 ± 4	137 ± 3	29 ± 2	97
10.00	5/5	108 ± 2	135 ± 2	28 ± 1*	96
20.00	5/5	108 ± 3	128 ± 3*	20 ± 3**	91

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Day of death: 4, 5

TABLE 3
Incidences and Severity of Nephropathy in Rats in the 16-Day Gavage Studies of Mercuric Chloride

	Vehicle Control	1.25 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
Male						
Nephropathy	0/5	0/5	0/5	3/5	5/5**	5/5**
Minimal	0/5	0/5	0/5	3/5	3/5	0/5
Mild	0/5	0/5	0/5	0/5	2/5	2/5
Moderate	0/5	0/5	0/5	0/5	0/5	3/5
Female						
Nephropathy	0/5	0/5	0/5	1/5	3/5	5/5**
Minimal	0/5	0/5	0/5	1/5	3/5	1/5
Mild	0/5	0/5	0/5	0/5	0/5	4/5*

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$

6-Month Studies

All rats survived to study end (Table 4). The final mean body weights of the 5 mg/kg males and all dosed females were significantly less than but within 10% of the controls. Absolute and relative kidney weights were significantly increased in dosed males and in females receiving 0.625 mg/kg mercuric chloride or greater (Table F2). No other biologically significant differences in body or organ weights occurred.

Clinical chemistry parameters were determined at 2, 4, and 6 months (Table G1). At 4 months, creatinine and potassium levels and alanine aminotransferase and aspartate aminotransferase activities were significantly less than those of the controls for all dosed males. No other biologically significant differences in clinical chemistry parameters were observed.

Mercury levels in kidney, liver, and brain tissues tended to increase with dose. Mercury levels were highest in the kidney and lowest in the brain (Table I2). Mercury levels in males and females tended to be similar.

At necropsy, macroscopic changes in dosed males included granular kidneys and enlargement of the parathyroid and thyroid glands. No biologically significant changes were noted at necropsy for dosed females. Chemical-related histopathologic changes included an increase in the severity of nephropathy (Table 5). Nephropathy was characterized by foci of tubule regeneration, basement membrane thickening, and scattered dilated tubules containing hyaline casts.

Dose selection rationale: Based on body weight changes and renal toxicity, the dose levels of mercuric chloride selected for administration by gavage to male and female rats for the 2-year studies were 0, 2.5, and 5 mg/kg.

TABLE 4
Survival and Mean Body Weights of Rats in the 6-Month Gavage Studies of Mercuric Chloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0.000	10/10	147 ± 6	436 ± 9	288 ± 5	–
0.312	10/10	149 ± 6	437 ± 6	287 ± 4	100
0.625	10/10	151 ± 6	416 ± 9	266 ± 7	95
1.250	10/10	137 ± 5	425 ± 9	288 ± 7	98
2.500	10/10	147 ± 6	422 ± 9	275 ± 7	97
5.000	10/10	146 ± 6	406 ± 9*	260 ± 7**	93
Female					
0.000	10/10	124 ± 4	240 ± 3	116 ± 3	–
0.312	10/10	119 ± 3	229 ± 3*	110 ± 3	95
0.625	10/10	124 ± 3	232 ± 3*	108 ± 3*	97
1.250	10/10	122 ± 4	226 ± 4**	104 ± 2**	94
2.500	10/10	123 ± 4	223 ± 3**	100 ± 3**	93
5.000	10/10	127 ± 4	223 ± 3**	96 ± 3**	93

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

TABLE 5
Incidences and Severity of Nephropathy in Rats in the 6-Month Gavage Studies of Mercuric Chloride

	Vehicle Control	0.312 mg/kg	0.625 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
Male						
Nephropathy	8/10	10/10	10/10	10/10	10/10	10/10
Minimal	8/10	10/10	9/10	6/10	7/10	6/10
Mild	0/10	0/10	1/10	4/10*	3/10	4/10*
Female						
Nephropathy	0/10	0/10	1/10	1/10	0/10	4/10*
Minimal	0/10	0/10	1/10	1/10	0/10	4/10*

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test

2-Year Studies

15-Month Interim Evaluations

In dosed rats, relative kidney weights were significantly increased; relative brain weights were significantly increased in dosed females (Table F3). In high-dose females, absolute liver weights were significantly lower while relative liver weights were significantly higher than those of the controls; these changes were considered secondary to the lower body weight in this group. The severity of nephropathy was increased in male rats at 15 months and was similar to nephropathy in the 6-month study animals (Table 6). In high-dose rats, the forestomach epithelium increased in thickness from one to several cell layers (acanthosis). The change was diffuse with focal areas of more severe acanthosis.

TABLE 6
Incidences and Severity of Selected Lesions in Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Mercuric Chloride

Diagnosis	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
Kidney			
Nephropathy	10/10	10/10	10/10
Minimal[a]	2	0	0
Mild	7	5	1
Moderate	1	5	6
Marked	0	0	3
Mean ± standard error	1.9 ± 0.18	2.5 ± 0.17*	3.2 ± 0.20**
Stomach, forestomach			
Acanthosis	0/10	0/10	10/10**
Minimal	0	0	6
Mild	0	0	4
Female			
Stomach, forestomach			
Acanthosis	0/10	0/10	5/10*
Minimal	0	0	5

* Significantly different (P≤0.05) from the control group by Mann-Whitney U test (average severity grade) or Fisher's exact test (incidence)
** P≤0.01
[a] Minimal=1, mild=2, moderate=3, marked=4

Survival

Survival of dosed male rats was significantly lower than that of the controls and was related to mercuric chloride administration (Table 7). Of the high-dose male rats that died prior to study end, 38/45 (84%) had moderate to marked nephropathy, which probably contributed to the decreased survival rates in this group. Kaplan-Meier survival probabilities for both male and female rats are presented in Figure 1.

Body Weights and Clinical Findings

Body weights of low-dose males were 11% to 16% lower than controls after week 91; body weights of low-dose females were generally similar to controls throughout the 2-year study (Figure 2, Tables 8 and 9). During the second year of the studies, body weights of high-dose males were 11% to 22% lower than controls and body weights of high-dose females were 11% to 16% lower. No other clinical findings were attributed to mercuric chloride administration.

TABLE 7
Survival of Rats in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	4	21	13
Moribund	20	19	32
15-month interim evaluation[a]	10	10	10
Animals surviving to the end of the study	26	10	5
Percent probability of survival at end of study[b]	52	21	10
Mean survival days[c]	641	563	586
Survival analyses[d]	P<0.001	P<0.001	P<0.001
Female			
Animals initially in study	60	60	60
Natural deaths	1	7	11
Moribund	14	14	9
15-month interim evaluation[a]	10	10	10
Missexed[a]		1	
Died last week of study		1	1
Animals surviving to the end of the study	35	27	29
Percent probability of survival at end of study	70	58	61
Mean survival days	658	623	612
Survival analyses	P=0.271	P=0.210	P=0.305

[a] Censored from survival analyses
[b] Kaplan-Meier determinations. Survival rates adjusted for missexed animals and for interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The entry under the "Vehicle Control" column is associated with the life table trend test (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972).

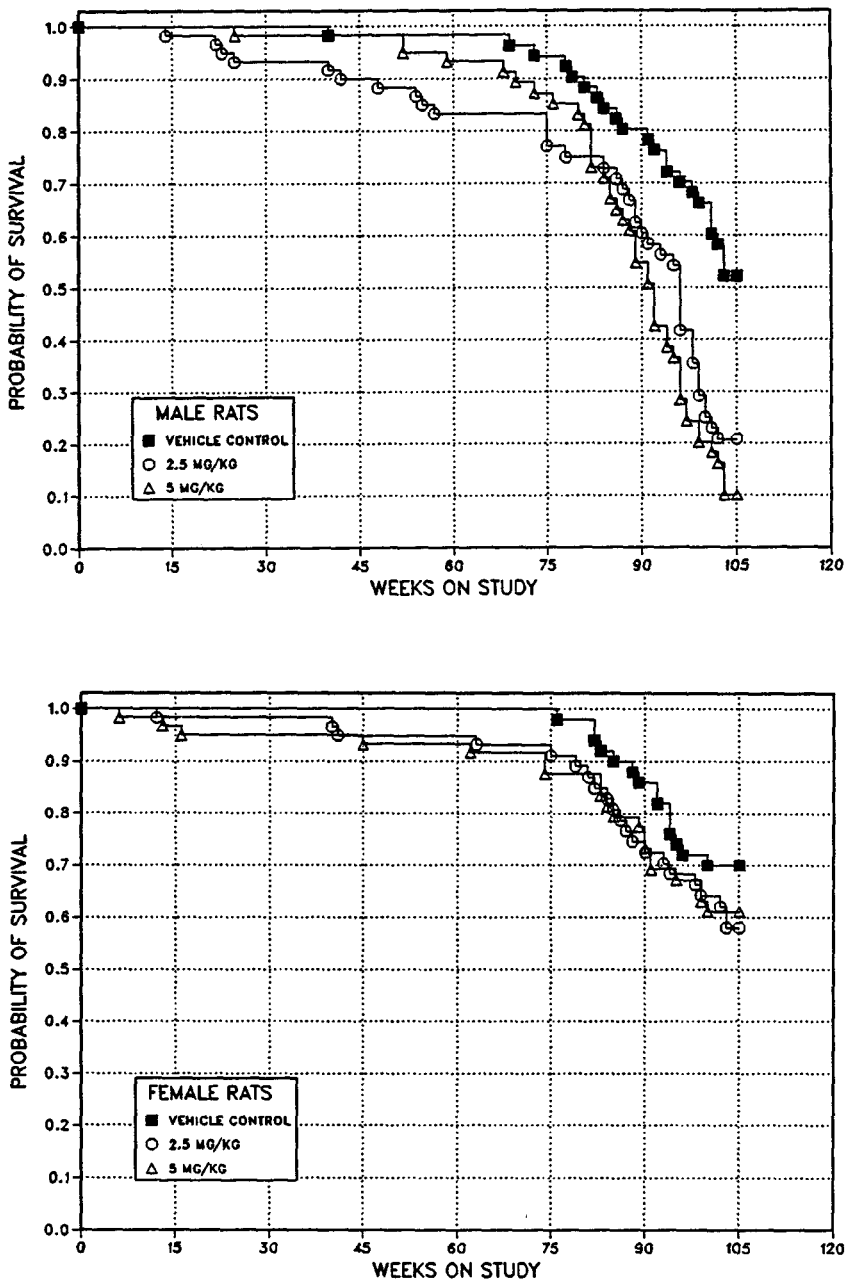

FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Mercuric Chloride by Gavage for 2 Years

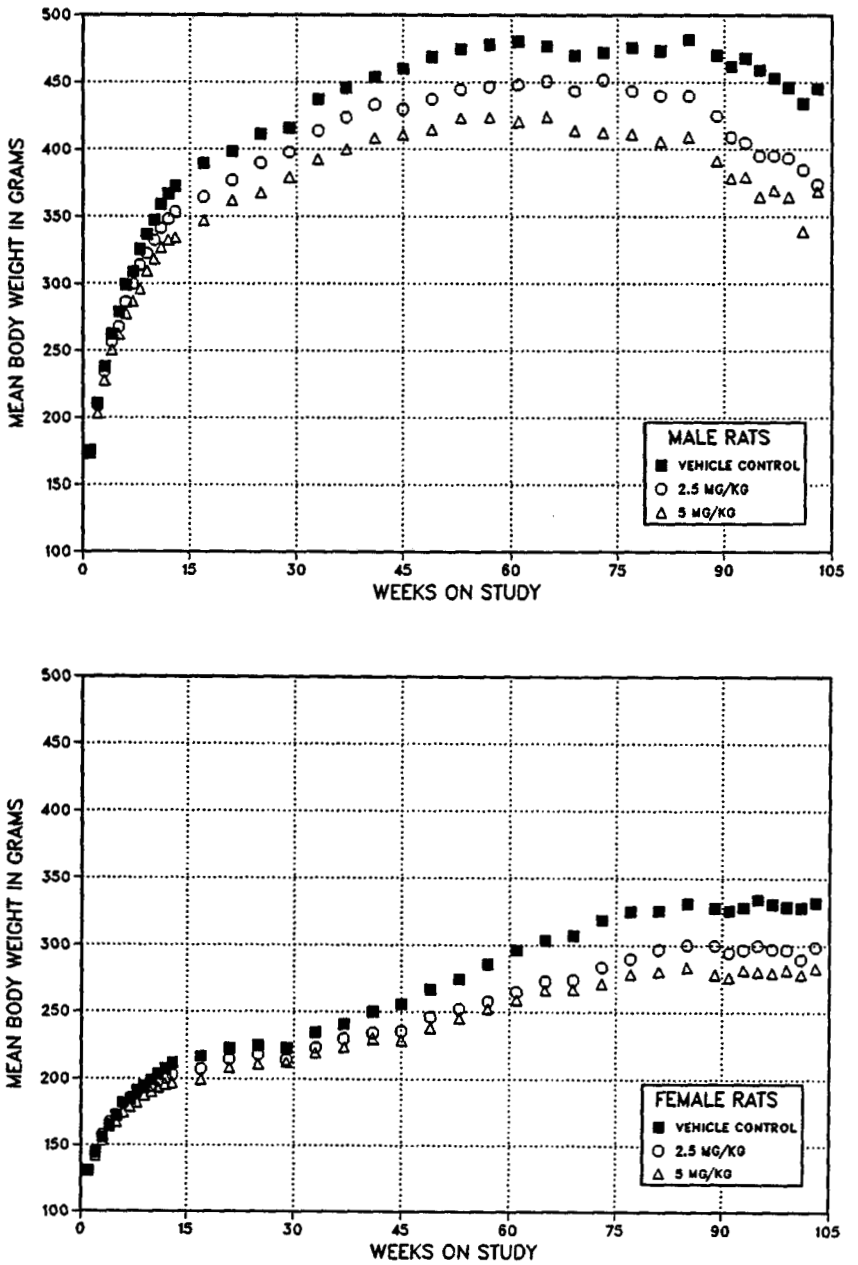

FIGURE 2
Growth Curves for Male and Female Rats Administered Mercuric Chloride by Gavage for 2 Years

TABLE 8
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Mercuric Chloride

Weeks on Study	Vehicle Control		2.5 mg/kg			5 mg/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors
1	159	60	158	99	60	158	99	60
2	211	60	209	99	60	203	96	60
3	238	60	234	98	60	228	96	60
4	262	60	257	98	60	250	96	60
5	279	60	268	96	60	263	94	60
6	299	60	286	96	60	278	93	60
7	309	60	300	97	60	287	93	60
8	326	60	314	96	60	296	91	60
9	337	60	323	96	60	310	92	60
10	348	60	333	96	60	318	92	60
11	359	60	341	95	60	327	91	60
12	367	60	348	95	60	333	91	60
13	373	60	354	95	60	335	90	60
17	389	60	365	94	59	347	89	60
21	398	60	377	95	59	362	91	60
25	411	60	390	95	56	368	89	59
29	416	60	398	96	56	379	91	59
33	437	60	414	95	56	393	90	59
37	446	60	424	95	56	400	90	59
41	454	59	433	96	55	409	90	59
45	460	59	430	94	54	411	89	59
49	469	59	437	93	53	415	89	59
53	475	59	445	94	53	423	89	57
57	478	59	447	93	50	424	89	57
61	480	59	448	93	50	421	88	56
65	477	59	451	95	50	424	89	56
69[a]	470	48	443	94	40	414	88	45
73	472	47	452	96	40	413	88	43
77	476	47	443	93	37	412	86	42
81	473	44	440	93	36	406	86	40
85	482	42	440	91	35	409	85	33
89	470	40	425	90	30	392	83	28
91	462	39	409	89	28	379	82	25
93	468	38	405	87	28	380	81	21
95	459	36	395	86	26	365	80	18
97	453	35	395	87	20	370	82	12
99	446	33	393	88	14	365	82	10
101	434	31	385	89	11	339	78	9
103	445	26	374	84	10	369	83	5
Terminal sacrifice		26			10			5
Mean for weeks								
1-13	297		287	97		276	93	
14-52	431		408	95		387	90	
53-103	466		423	91		394	85	

[a] Interim evaluation occurred.

TABLE 9
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Mercuric Chloride

Weeks on Study	Vehicle Control		2.5 mg/kg			5 mg/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors
1	122	60	122	100	60	121	99	60
2	145	60	146	101	59	142	98	60
3	156	60	158	101	59	153	98	60
4	166	60	167	101	59	164	99	60
5	172	60	173	100	59	168	97	60
6	182	60	181	100	59	175	96	59
7	185	60	186	101	59	179	97	59
8	191	60	190	99	59	182	95	59
9	195	60	194	100	59	187	96	59
10	199	60	194	98	59	190	96	59
11	204	60	198	97	59	194	95	59
12	208	60	200	97	58	196	95	59
13	212	60	203	96	58	197	93	58
17	217	60	208	96	58	200	92	57
21	223	60	215	96	58	208	93	57
25	225	60	218	97	58	211	94	57
29	223	60	215	96	58	213	95	57
33	235	60	224	95	58	220	94	57
37	241	60	230	95	58	224	93	57
41	250	60	234	94	56	230	92	57
45	256	60	236	92	56	229	90	56
49	267	60	246	92	56	238	89	56
53	275	60	252	92	56	246	89	56
57	286	60	258	90	56	253	88	56
61	296	60	265	90	56	259	87	56
65	303	60	273	90	55	266	88	55
69[a]	308	50	274	89	45	267	87	45
73	319	50	284	89	45	272	85	45
77	325	49	290	89	44	279	86	43
81	326	49	297	91	42	281	86	43
85	332	45	300	91	39	284	86	39
89	328	43	300	92	36	279	85	39
91	326	43	295	90	35	277	85	34
93	329	41	297	90	34	282	86	34
95	334	37	300	90	33	281	84	33
97	331	36	298	90	33	280	85	33
99	329	36	297	90	31	282	86	31
101	329	35	290	88	31	279	85	30
103	332	35	299	90	28	283	85	30
Terminal sacrifice		35			28			30
Mean for weeks								
1-13	180		178	99		173	96	
14-52	237		225	95		219	92	
53-103	318		286	90		274	86	

[a] Interim evaluation occurred.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the kidney, forestomach, thyroid gland, mammary gland, and nasal cavity in rats.

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

Kidney: Nephropathy occurred in nearly all male rats including the controls, but the severity of nephropathy was significantly increased in males receiving mercuric chloride (Table 10). The severity of nephropathy was not increased in dosed females. Nephropathy is a spontaneous, age-related disease that is characterized by thickening of glomerular and tubular basement membranes, glomerular sclerosis, degeneration and atrophy of the renal tubule epithelium with tubule dilatation and cast formation, regeneration of the tubule epithelium, interstitial fibrosis, and chronic inflammation. The severity of nephropathy was graded from minimal (less than 25% of renal tubules affected) to marked (greater than 75% of the tubules affected). Chemicals toxic to the proximal tubules often exacerbate the complex of lesions that compose this chronic renal disease. The increased severity of nephropathy in dosed males resulted in sufficient functional impairment to increase the incidence of parathyroid gland hyperplasia and the changes associated with hyperparathyroidism, including fibrous osteodystrophy and mineralization of several tissues.

In the initial evaluation of single sections from the left and right kidneys, focal hyperplasia or adenoma

TABLE 10
Nephropathy Severity in Rats in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
Overall rates	50/50 (100%)	46/50 (92%)	48/50 (96%)
Nephropathy[a]			
None	0	4	2
Minimal	3	3	2
Mild	17	4	3
Moderate	24	10	14
Marked	6	29	29
Average severity grade	2.66 ± 0.11	3.14 ± 0.18**	3.32 ± 0.15**
Female			
Overall rates	49/50 (98%)	43/49 (88%)	41/50 (82%)
Nephropathy			
None	1	6	9
Minimal	28	27	23
Mild	17	13	13
Moderate	4	3	5
Marked	0	0	0
Average severity grade	1.48 ± 0.10	1.27 ± 0.11	1.28 ± 0.12

** Significantly different ($P \leq 0.01$) from the control group by Mann-Whitney U test
[a] None=0, Minimal=1, mild=2, moderate=3, marked=4

of the renal tubule occurred in a few male and female rats. Step sections of kidneys from both control and high-dose rats revealed a few more hyperplasias and adenomas (Table 11). The historical incidence of renal tubule neoplasms in water gavage control male rats is 2/263 (0.8%) with a range of 0% to 3% (Table A4a); the historical incidence in water gavage control female rats is 0/265 (Table B4a).

Focal hyperplasia of the renal tubule epithelium was distinguished from the epithelial regeneration commonly seen in aged rats with nephropathy by multiple layers of epithelial cells within the tubule, by increased size of the renal tubule epithelial cells, by increased size and variability of the nuclei, and by occasional mitotic figures. A morphologic continuum exists for focal hyperplasia, adenoma, and carcinoma. Focal hyperplasia consisted of one or more cross-sections of tubules in the cortex partially or completely filled with stratified epithelial cells. Adenomas were distinguished from hyperplasia primarily on the basis of size (generally larger than three tubules) and cytologic atypia.

TABLE 11
Selected Kidney Lesions in Rats in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
Initial Evaluation (Single Sections)			
Renal Tubule Hyperplasia			
Overall rates[a]	1/50 (2%)	1/50 (2%)	5/50 (10%)
Logistic regression[b]	P=0.041	P=0.710	P=0.107
Renal Tubule Adenoma[c]			
Overall rates	0/50 (0%)	2/50 (4%)	0/50 (0%)
Logistic regression	P=0.556	P=0.160	–[d]
Evaluation of Step Sections			
Renal Tubule Hyperplasia			
Overall rates	2/50 (4%)	–[e]	8/50 (16%)
Logistic regression	–		P=0.014
Renal Tubule Adenoma			
Overall rates	4/50 (8%)		5/50 (10%)
Logistic regression	–		P=0.231
Single and Step Sections Combined			
Renal Tubule Hyperplasia			
Overall rates	3/50 (6%)		12/50 (24%)[f]
Logistic regression	–		P=0.005
Renal Tubule Adenoma			
Overall rates	4/50 (8%)		5/50 (10%)
Logistic regression	–		P=0.231

(continued)

TABLE 11
Selected Kidney Lesions in Rats in the 2-Year Gavage Studies of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Female			
Initial Evaluation (Single Sections)			
Renal Tubule Hyperplasia			
Overall rates	0/50 (0%)	1/49 (2%)	2/50 (4%)
Logistic regression	P=0.141	P=0.549	P=0.225
Renal Tubule Adenoma[g]			
Overall rates	0/50 (0%)	0/49 (0%)	1/50 (2%)
Logistic regression	P=0.259	–	P=0.485
Evaluation of Step Sections			
Renal Tubule Hyperplasia			
Overall rates	2/50 (4%)		3/50 (6%)
Logistic regression	–		P=0.438
Renal Tubule Adenoma			
Overall rates	0/50 (0%)		1/50 (2%)
Single and Step Sections Combined			
Renal Tubule Hyperplasia			
Overall rates	2/50 (4%)		5/50 (10%)
Logistic regression	–		P=0.169
Renal Tubule Adenoma			
Overall rates	0/50 (0%)		2/50 (4%)
Logistic regression			P=0.211

(T) Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals examined microscopically
[b] 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 test regards these lesions as nonfatal.
[c] Historical incidence for 2-year water gavage studies with vehicle control groups (mean ± standard deviation): 2/263 (0.8% ± 1.3%); range 0%-3%.
[d] Value of statistic cannot be computed
[e] No step sections examined in males or females in this dose group
[f] Some animals had multiple hyperplasias.
[g] Historical incidence for 2-year water gavage studies with vehicle control groups: 0/265

Forestomach: The incidence of hyperplasia of the stratified squamous epithelium lining the forestomach was significantly increased in dosed males and in high-dose females (Table 12). Squamous cell papillomas also occurred with significantly increased incidence in high-dose males; papillomas occurred in two high-dose females. Squamous cell papillomas of the forestomach are rare neoplasms in rats and have occurred in 1/264 (0.4%) water gavage historical control males (Table A4b). No squamous cell papillomas have been seen in water gavage control females (Table B4b). No squamous cell carcinomas were observed in these 2-year studies.

Papillary hyperplasia consisted of one or more foci of thickened stratified squamous epithelium forming raised papillary projections (Plate 1). The squamous cell papillomas differed from hyperplasia by having a central fibrovascular stalk with complex branching fronds covered by thickened stratified epithelium (Plate 2). The increased thickness of the stratum spinosum was often accompanied by increased numbers of basal cells, but there was no evidence of invasion or of cellular atypia.

Thyroid Gland: The incidence of follicular cell carcinoma was marginally increased in high-dose male

TABLE 12
Incidence of Selected Lesions of the Forestomach in Rats in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
Papillary Hyperplasia			
Overall rates[a]	3/49 (6%)	16/50 (32%)**	35/50 (70%)**
Squamous Cell Papilloma[b]			
Overall rates	0/50 (0%)	3/50 (6%)	12/50 (24%)
Single	0/50 (0%)	2/50 (4%)	6/50 (12%)
Multiple	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted rates[c]	0.0%	17.7%	66.3%
Terminal rates[d]	0/26 (0%)	1/10 (10%)	2/5 (40%)
First incidence (days)	–[f]	664	490
Logistic regression tests[e]	P<0.001	P=0.066	P<0.001
Female			
Papillary Hyperplasia			
Overall rates	5/50 (10%)	5/49 (10%)	20/50 (40%)**
Squamous Cell Papilloma[g]			
Overall rates	0/50 (0%)	0/49 (0%)	2/50 (4%)

** Significantly different (P≤0.01) from the control group by logistic regression analysis
[a] Number of lesion-bearing animals/number of animals examined microscopically.
[b] Historical incidence for 2-year NTP water gavage study vehicle control groups (mean ± standard deviation): 1/264 (0.4% ± 0.9%); range 0%-2%.
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the "Vehicle Control" column 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 test regards these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence: 0/265

rats (Table 13). However, the overall incidence of follicular cell neoplasms (adenoma or carcinoma combined) was not significantly increased (2/50, 6/50, 6/50), and there was no increased incidence in follicular cell hyperplasia (2/50, 4/50, 2/50). The historical incidence of thyroid follicular cell carcinoma in water gavage control male rats (1/259, 0.4%) is the same as the historical incidence of follicular cell adenoma in water gavage control male rats (Table A4c).

Focal follicular cell hyperplasia, adenoma, and carcinoma constitute a morphological continuum. In the present studies, follicular cell hyperplasia was a focal lesion which often appeared near the margin of the gland. The lesion consisted of papillary foldings of the single-layered epithelium into the lumen of one or more follicles. Cystic distention of the follicular lumens was present in some lesions. The distinction between adenoma and hyperplasia was not always clear. Adenomas were circumscribed masses of follicular and/or papillary structures restricted to the thyroid gland; the epithelium was generally uniform and well differentiated. Follicular cell carcinomas were generally large, sometimes obliterating the entire gland, and scirrhous. The carcinomas generally exhibited greater cellular pleomorphism and atypia than did the adenomas.

TABLE 13
Incidences of Selected Thyroid Follicular Cell Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Hyperplasia			
Overall rates[a]	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adenoma			
Overall rates	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rates[b]	3.8%	18.3%	0.0%
Terminal rates[c]	1/26 (4%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	627	–[e]
Logistic regression tests[d]	P=0.490N	P=0.116	P=0.821N
Carcinoma			
Overall rates	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rates	3.8%	11.6%	31.9%
Terminal rates	1/26 (4%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	671	569
Logistic regression tests	P=0.017	P=0.368	P=0.044
Adenoma or Carcinoma[f]			
Overall rates	2/50 (4%)	6/50 (12%)	6/50 (12%)
Adjusted rates	7.7%	27.7%	31.9%
Terminal rates	2/26 (8%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	627	569
Logistic regression tests	P=0.062	P=0.061	P=0.091

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column 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 test regards these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] Historical incidence in 2-year NTP water gavage study vehicle control groups (mean ± standard deviation): 4/259 (1.5% ± 2.2%); range 0%-5%; includes data for two adenocarcinomas.

Nasal Cavity: An increase in the incidences of nasal mucosa inflammatory lesions occurred in males (9/50, 8/47, 18/50; Table A5) and females (0/49, 5/49, 15/50; Table B5). The inflammation was generally focal or multifocal and was characterized primarily by a few neutrophils present in the lumen and mucosa of the respiratory epithelium.

Parathyroid Gland: Systemic effects, such as hyperparathyroidism, which may be seen histologically as parathyroid hyperplasia, were secondary to marked renal impairment. Hyperplasia was seen in the parathyroid glands of dosed male rats, but not of dosed female rats, which had less severe nephropathy. The incidence of hyperplasia in dosed males (2/49, 25/44, 19/49; Table A5) was much higher than the incidence of hyperplasia in dosed females (1/47, 1/49, 0/45; Table B5).

Pituitary Gland: The incidence of male rats with hyperplasia (12/50, 9/49, 6/50) or adenoma (14/50, 4/49, 4/50) of the pars distalis decreased with dose. No carcinomas were found in dosed male rats, but one carcinoma was found in a control male (Table A1). This decrease may have been related to the decreased survival in the treated males or secondary to the decreased weight gain.

Mammary Gland: The incidence of mammary gland fibroadenomas in female rats significantly decreased with dose (Table 14). This decrease may have been related to the lower body weight gain in the treated females.

Bone: Dosed male rats showed an increased incidence in fibrous osteodystrophy (1/50, 27/49, 21/50; Table A5), which was thought to be secondary to severe renal disease. Fibrous osteodystrophy was not diagnosed in female rats. Fibrous osteodystrophy usually involved the long bones but was also seen in the bones of the skull. It was characterized by an increase in osteoclasts and Howship's lacunae, atrophy of the trabeculae, and proliferation of connective tissue in the marrow space.

Heart: Focal or multifocal mineralization of the heart was significantly increased in dosed male rats (0/50, 13/50, 14/50; Table A5); this lesion usually accompanies renal impairment and hyperparathyroidism.

TABLE 14
Mammary Gland Fibroadenomas in Female Rats in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Fibroadenoma[a]			
Overall rates[b]	15/50 (30%)	5/48 (10%)	2/50 (4%)
Adjusted rates[c]	35.8%	16.7%	6.7%
Terminal rates[d]	9/35 (26%)	4/28 (14%)	2/30 (7%)
First incidence (days)	576	629	729 (T)
Logistic regression tests[e]	P<0.001N	P=0.020N	P=0.001N

(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP water gavage study vehicle control groups (mean ± standard deviation): 101/265 (38.1% ± 14.8%); range 16%-53%
[b] Number of neoplasm-bearing animals/number of animals examined at site
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the "Vehicle Control" column 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 test regards these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

MICE

16-Day Studies

All male and four female mice given 80 mg mercuric chloride/kg body weight died within the first week of dosing (Table 15). One male mouse in the 40 mg/kg group died on day 4. Final mean body weights and mean body weight gains of dosed mice were similar to those of the controls. Both absolute and relative kidney weights in dosed males and relative kidney weights in dosed females were significantly greater than those of the controls (Table F4). In females, absolute and relative liver weights were significantly decreased at the 40 mg/kg dose level; relative brain weights at 10, 20, or 40 mg/kg were significantly increased. Absolute thymus weights were significantly decreased in females receiving 20 or 40 mg/kg. No other biologically significant differences in body or organ weights were observed.

Kidney, liver, and brain tissues of male and female mice from the control and 40 mg/kg groups were analyzed for mercury concentrations (Table I3). Tissues of the control groups contained less than 0.5 ppm mercury. Mercury concentrations in kidney tissues from the 40 mg/kg groups were 171 ppm for males and 116 ppm for females; concentrations in liver tissues were 35 and 29 ppm for males and females, respectively. Mercury concentrations in brain tissue from the 40 mg/kg groups of each sex were less than 1 ppm.

The most prominent histopathologic finding was acute renal tubule necrosis, which was observed in all male and female mice receiving 80 mg/kg and two males receiving 40 mg/kg mercuric chloride. Inflammation and necrosis of the forestomach and necrosis of the glandular stomach also occurred in some high-dose mice.

TABLE 15
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of Mercuric Chloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)
Male					
0	5/5	23.2 ± 1.0	25.0 ± 0.8	1.8 ± 0.2	–
5	5/5	23.2 ± 0 4	24.4 ± 0.4	1.2 ± 0.4	98
10	5/5	23.2 ± 1.0	24.6 ± 0.8	1.4 ± 0.2	98
20	5/5	23.8 ± 0.6	25.4 ± 0.9	1.6 ± 0.4	102
40	4/5[c]	23.0 ± 0.6	23.8 ± 1.7	0.8 ± 1.0	95
80	0/5[d]	23.2 ± 0.6	–	–	–
Female					
0	5/5	17.8 ± 0.5	20.2 ± 0.5	2.4 ± 0.5	
5	5/5	17.6 ± 0.6	19.8 ± 0.5	2.2 ± 0.2	98
10	5/5	17.8 ± 0.2	20.2 ± 0.4	2.4 ± 0.2	100
20	5/5	18.4 ± 0.6	20.8 ± 0.4	2.4 ± 0.2	103
40	5/5	18.0 ± 0.5	20.4 ± 0.6	2.4 ± 0.5	101
80	1/5[e]	18.0 ± 0.5	21.0[f]	2.0	104

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. Differences from the control group are not significant by Williams' or Dunnett's test. No final mean body weights or weight changes were calculated for groups with 100% mortality.
[c] Day of death: 4
[d] Day of death: 2, 3, 4, 4, 4
[e] Day of death: 3, 4, 4, 4
[f] No standard error was calculated due to high mortality in this group.

6-Month Studies

No chemical-related deaths occurred during these studies. One male and one female died as the result of gavage accidents in week 2. The final mean body weight and body weight gain of males in the 20 mg/kg group were significantly less than those of the controls (Table 16). Final mean body weights and body weight gains of all other dose groups were similar to those of the controls. Significant increases occurred in absolute kidney weights of male mice receiving 5 mg/kg or greater and in relative kidney weights of male mice receiving 10 or 20 mg/kg (Table F5). Significant decreases in absolute brain, heart, and liver weights were considered secondary to decreases in body weight. No other biologically significant differences in organ weights were observed.

Clinical chemistry tests were performed at 2, 4, and 6 months (Table G3), and no biologically significant differences were observed. Kidney and liver tissues from the vehicle control, 1.25, 5, and 20 mg/kg groups, and brain tissue from vehicle control and 20-mg/kg groups were analyzed for mercury residue levels at 2, 4 and 6 months (Table I4). Mercury residue levels tended to increase with dose. In each sex, mercury concentrations were highest in the kidney and lowest in the brain.

The incidence and severity of cytoplasmic vacuolation of renal tubule epithelium increased in male mice in the 5, 10, and 20 mg/kg groups. Chemical-related changes were not found in the kidneys of female mice.

Dose selection rationale: Based on body weight changes and renal toxicity, the dose levels of mercuric chloride selected for administration by gavage to male and female mice for the 2-year studies were 0, 5, and 10 mg/kg body weight. Administration of 20 mg/kg, especially to males, was expected to cause excessive toxicity and decreased survival.

TABLE 16
Survival and Mean Body Weights of Mice in the 6-Month Gavage Studies of Mercuric Chloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0.00	10/10	22.1 ± 0.6	33.9 ± 1.0	11.8 ± 0.5	–
1.25	10/10	21.0 ± 0.5	35.5 ± 1.1	14.5 ± 0.9	105
2.50	10/10	21.8 ± 0.5	34.9 ± 1.1	13.1 ± 0.8	103
5.00	9/10[c]	21.9 ± 0.6	35.3 ± 1.2	13.3 ± 0.9	104
10.00	10/10	22.2 ± 0.4	32.0 ± 0.6	9.8 ± 0.5	94
20.00	10/10	21.0 ± 0.5	29.7 ± 1.0**	8.7 ± 0.7**	88
Female					
0.00	10/10	17.5 ± 0.4	27.2 ± 0.9	9.7 ± 0.8	–
1.25	10/10	17.6 ± 0.5	27.9 ± 1.4	10.3 ± 1.1	103
2.50	10/10	17.4 ± 0.4	27.6 ± 1.1	10.2 ± 0.9	101
5.00	9/10[c]	17.0 ± 0.4	26.8 ± 1.1	9.9 ± 0.9	98
10.00	10/10	17.5 ± 0.3	25.0 ± 0.7	7.5 ± 0.5	92
20.00	10/10	18.1 ± 0.6	27.3 ± 0.9	9.2 ± 0.8	100

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Week of death: 2, due to gavage accident

2-Year Studies

15-Month Interim Evaluations

Absolute kidney weights were significantly increased in dosed male mice; relative kidney weights were significantly increased in dosed female mice (Table F6). No other biologically significant differences in organ weights were observed.

In the kidneys of control mice, particularly males, clear cytoplasmic vacuoles (possibly containing lipids) were visible primarily within the proximal convoluted tubules. The severity of cytoplasmic vacuolation in the renal tubule epithelium increased in dosed male mice (Table 17). The renal tubule epithelium of controls had few cytoplasmic vacuoles, whereas in dosed males, the vacuoles were more numerous and larger. Also, an increased number of tubules was affected, and the cytoplasmic vacuolation of epithelium extended more deeply into the cortex in dosed males than in controls. Similar changes were not found in the kidneys of female mice.

In mice receiving 10 mg mercuric chloride/kg body weight, the incidences of inflammation and of metaplasia of the olfactory epithelium in the nasal mucosa were increased. Metaplasia of the olfactory epithelium was characterized by the focal replacement of the olfactory epithelium by ciliated columnar epithelium in the dorsal meatus, in the dorsal area of the nasal septum, and on the medial surface of the dorsal portion of the nasal turbinate. This change is often referred to as respiratory metaplasia of the olfactory epithelium. In these studies, the metaplasia was usually found only in the most anterior region of the olfactory epithelium near the margin between the olfactory and respiratory epithelium. The Bowman's glands beneath this area also contained ciliated epithelium. In some animals the underlying Bowman's glands showed hyperplasia, epithelial alteration, and cytoplasmic hyaline granules. The inflammation was characterized by focal accumulations of neutrophils and cellular debris in the mucosa and lumens of scattered Bowman's glands. No chemical-related neoplasms were found.

TABLE 17
Renal Tubule Vacuolation in Male Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Mercuric Chloride

Vacuolation	Vehicle Control	5 mg/kg	10 mg/kg
Minimal	9	5	1
Mild	1	5	8
Moderate	0	0	1
Total	10	10	10

Survival

Survival of male mice was unaffected by the administration of mercuric chloride; however, survival of high-dose females was slightly lower than the controls (Table 18). Kaplan-Meier survival probabilities are presented for male and female mice in Figure 3.

Body Weights and Clinical Findings

Mean body weights of dosed male and female mice were within 10% of controls throughout the studies (Tables 19 and 20 and Figure 4). No clinical findings attributed to mercuric chloride were observed during the 2-year studies.

TABLE 18
Survival of Mice in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	5 mg/kg	10 mg/kg
Male			
Animals initially in study	60	60	60
Natural deaths	8	10	8
Moribund	6	4	11
15-month interim evaluation[a]	10	10	10
Animals surviving to the end of the study	36[b]	36	31
Percent probability of survival at end of study[c]	74	75	64
Mean survival days[d]	591	591	567
Survival analyses[e]	P=0.339	P=0.873	P=0.398
Female			
Animals initially in study	60	60	60
Natural deaths	5	4	10
Moribund	4	11	8
15-month interim evaluation[a]	10	10	10
Accidental deaths[a]			1
Animals surviving to the end of the study	41	35	31
Percent probability of survival at end of study	82	71	64
Mean survival days	662	650	623
Survival analyses	P=0.038	P=0.251	P=0.051

[a] Censored from survival analyses
[b] Includes one animal that died last week of study
[c] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim evaluations.
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] The entry under the "Vehicle Control" column is associated with the life table trend test (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972).

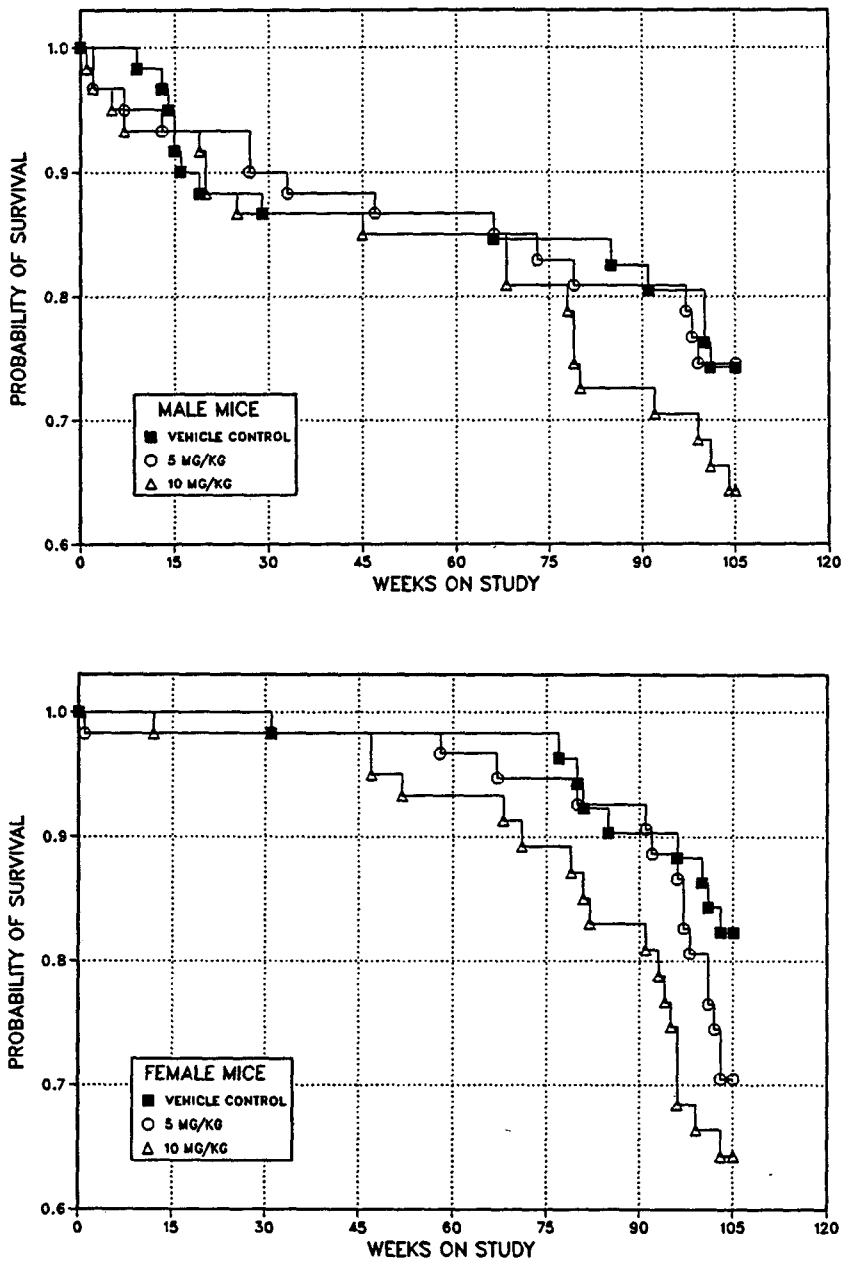

FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Mercuric Chloride by Gavage for 2 Years

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Mercuric Chloride

Weeks on Study	Vehicle Control		5 mg/kg			10 mg/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors
1	22.3	60	21.8	98	60	21.4	96	60
2	23.9	60	23.6	99	58	23.0	96	58
3	25.4	60	24.9	98	58	24.1	95	58
4	26.4	60	26.1	99	58	25.5	97	58
5	27.2	60	25.7	95	58	26.4	97	57
6	28.0	60	27.6	99	58	26.9	96	57
7	28.5	60	28.1	99	57	27.5	97	56
8	28.6	60	28.1	98	57	27.3	96	56
9	29.2	59	28.4	97	57	27.8	95	56
10	29.9	59	29.6	99	57	28.4	95	56
11	30.3	59	29.4	97	57	28.9	95	56
12	31.1	59	30.4	98	57	29.4	95	56
13	31.2	58	30.1	97	56	29.9	96	56
17	31.8	54	31.1	98	56	30.2	95	56
21	33.0	53	32.3	98	56	31.1	94	53
25	34.0	53	32.9	97	56	32.1	94	52
29	34.7	52	34.3	99	54	33.4	96	52
33	35.0	52	33.7	96	53	33.5	96	52
37	35.7	52	35.0	98	53	34.8	98	52
41	35.7	52	35.6	100	53	35.1	98	52
45	37.5	52	35.5	95	53	35.3	94	51
49	37.8	52	36.4	96	52	36.0	95	51
53	37.7	52	36.9	98	52	36.4	97	51
57	39.9	52	39.4	99	52	38.2	96	51
61	40.3	52	39.1	97	52	37.7	94	51
65	39.6	52	39.4	100	52	38.1	96	51
70[a]	39.8	41	39.0	98	41	38.0	96	39
73	40.7	41	40.5	100	40	39.8	98	39
77	40.1	41	39.1	98	40	38.9	97	39
81	40.1	41	38.6	96	39	38.8	97	35
85	39.3	41	38.8	99	39	38.3	98	35
89	38.1	40	37.9	100	39	37.4	98	35
91	38.1	40	37.9	100	39	37.5	98	35
93	38.6	39	38.1	99	39	37.4	97	34
95	38.4	39	38.5	100	39	37.6	98	34
97	37.5	39	37.6	100	38	37.0	99	34
99	35.7	39	37.0	104	36	36.8	103	33
100	30.3	37						
101	36.8	36	37.5	102	36	35.8	97	32
103	36.7	36	37.6	103	36	36.4	99	32
Terminal sacrifice		36			36			31
Mean for weeks								
1-13	27.8		27.2	98		26.7	96	
14-52	35.0		34.1	97		33.5	96	
52-103	38.2		38.4	101		37.7	99	

[a] Interim evaluation occurred.

TABLE 20
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Mercuric Chloride

Weeks on Study	Vehicle Control		5 mg/kg			10 mg/kg		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors	Av. Wt. (g)	Wt. (% of control)	Number of Survivors
1	17.9	60	17.6	98	60	17.2	96	60
2	19.1	60	19.0	100	59	18.8	98	60
3	20.3	60	19.7	97	59	19.3	95	60
4	21.5	60	20.5	95	59	20.4	95	60
5	22.0	60	21.4	97	59	20.4	93	60
6	22.1	60	22.1	100	59	21.1	96	60
7	22.9	60	22.2	97	59	21.5	94	60
8	22.7	60	22.1	97	59	21.2	93	60
9	22.9	60	22.5	98	59	21.4	93	60
10	23.6	60	23.1	98	59	22.2	94	60
11	23.9	60	23.5	98	59	22.2	93	60
12	24.1	60	23.4	97	59	22.8	95	59
13	24.0	60	23.7	99	59	22.6	94	59
17	25.2	60	24.3	96	59	23.8	94	59
21	26.0	60	25.6	99	59	24.2	93	59
25	27.4	60	26.5	97	59	25.3	92	59
29	29.0	60	27.8	96	59	27.2	94	59
33	29.3	59	28.5	97	59	27.7	95	59
37	30.1	59	29.4	98	59	29.0	96	59
41	30.3	59	29.9	99	59	28.9	95	59
45	31.9	59	31.2	98	59	30.5	96	59
49	32.8	59	32.1	98	59	31.2	95	57
53	34.0	59	31.9	94	59	31.1	92	56
57	35.7	59	34.4	96	59	32.1	90	56
61	35.0	59	34.3	98	58	32.1	92	56
65	35.4	59	34.8	98	58	32.9	93	55
70[a]	35.5	49	34.8	98	47	32.7	92	44
73	36.7	49	36.1	98	47	34.0	93	43
77	36.0	48	35.9	100	47	33.9	94	43
81	36.9	46	36.4	99	46	34.4	93	41
85	36.5	45	35.6	98	46	34.2	94	40
89	35.3	45	35.0	99	46	33.7	96	40
91	36.2	45	35.2	97	45	34.1	94	40
93	36.7	45	35.6	97	44	34.3	94	39
95	36.1	45	36.0	100	44	34.9	97	36
97	36.0	44	34.2	95	41	34.9	97	33
99	35.1	44	34.2	97	40	35.1	100	32
100	28.7	43						
101	35.9	42	34.4	96	38	34.5	96	32
103	34.6	41	32.7	95	35	34.8	101	31
Terminal sacrifice		41			35			31
Mean for weeks								
1-13	22.1		21.6	98		20.9	95	
14-52	29.1		28.4	98		27.5	95	
53-103	35.4		34.8	98		33.7	95	

[a] Interim evaluation occurred.

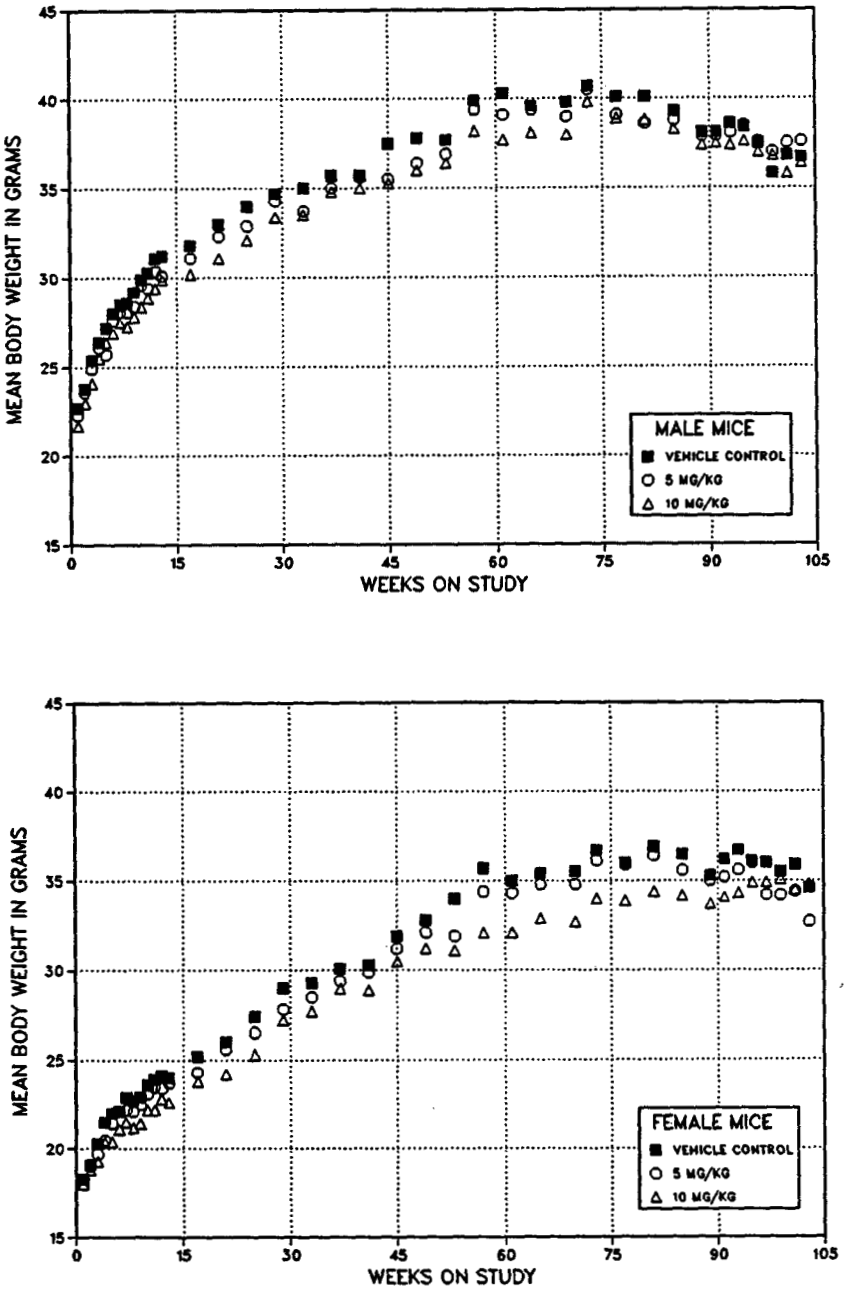

FIGURE 4
Growth Curves for Male and Female Mice Administered Mercuric Chloride by Gavage for 2 Years

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of the kidney, nasal cavity, and forestomach in mice.

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

Kidney: As with rats, the primary toxic changes occurred in kidneys. While the incidence of nephropathy was not significantly increased in male mice, the average severity of nephropathy increased from 1.08 to 2.51 (Table 21). In 33 of the high-dose males, the severity of nephropathy was either moderate or marked, whereas in most of the control males, severity was either minimal or mild. In female mice, both the incidence and severity of nephropathy were significantly increased by exposure to mercuric chloride.

The histologic appearance of nephropathy that occurred was similar in control and dosed mice. Nephropathy was characterized by focal collections of proximal convoluted tubules with thickened basement membranes and small basophilic cells having scant cytoplasm; some affected tubules contained hyaline (protein) casts. Focal collections of lymphocytes were found in the interstitium around tubules and small vessels. Occasional glomeruli had thickened basement membranes and dilatation of Bowman's space. The severity of nephropathy was judged as minimal, mild, moderate, or marked depending on the approximate number and extent of focal lesions observed in the kidney sections (minimal, 3 or fewer lesions; mild, 4 to 8 lesions; moderate, 8 to 12 lesions; marked, 12 or more lesions). Generally, in animals with moderate or marked nephropathy, more tubule profiles were affected in each focus and the extent of basement membrane thickening, interstitial fibrosis, and inflammation was greater. The increase in the degree and severity of cytoplasmic vacuolation observed at the 15-month interim evaluations was difficult to detect at the end of the 2-year studies due to aging changes and nephropathy. The Pathology Working Group felt vacuolation was present to a minor degree but it was not recorded as a separate diagnosis.

In the initial evaluation of single sections of kidney, focal hyperplasia of the renal tubule was observed in one control and two high-dose male mice. Renal tubule adenomas were found in two high-dose males, and an adenocarcinoma was found in a third (Table 21). The evaluation of step sections revealed focal hyperplasia in one additional control male; no additional renal tubule neoplasms were found. Hyperplasia or neoplasms of the kidney are uncommon in male mice. Renal tubule adenomas or adenocarcinomas occurred in 0/205 historical control males for water gavage studies.

Focal hyperplasia was characterized by slightly enlarged tubules containing two or more layers of epithelial cells. The two adenomas were found only during microscopic examination and were discrete circumscribed masses of polygonal epithelial cells (Plate 3). The adenocarcinoma occupied most of the pole of one kidney and was judged malignant on the basis of heterogeneity of growth pattern, cellular pleomorphism, and the presence of necrosis (Plate 4).

TABLE 21
Lesions of the Kidney and Nephropathy Severity in Mice in the 2-Year Gavage Studies of Mercuric Chloride

	Vehicle Control	5 mg/kg	10 mg/kg
Male			
Nephropathy			
Overall rates[a]	40/50 (80%)	45/50 (90%)	44/49 (90%)
Severity grade[b]			
None	10	5	5
Minimal	28	8	3
Mild	10	32	8
Moderate	2	5	28
Marked	0	0	5
Average severity grade	1.08	1.74**	2.51**
Renal Tubule Hyperplasia			
Overall rates	1/50 (2%)	0/50 (0%)	2/49 (4%)
Renal Tubule Adenoma			
Overall rates	0/50 (0%)	0/50 (0%)	2/49 (4%)
Renal Tubule Adenocarcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	1/49 (2%)
Renal Tubule Adenoma or Adenocarcinoma[c]			
Overall rates	0/50 (0%)	0/50 (0%)	3/49 (6%)
Adjusted rates[d]	0.0%	0.0%	9.1%
Terminal rates[e]	0/36 (0%)	0/36 (0%)	2/31 (6%)
First incidence (days)	–[g]	–	642
Logistic regression tests[f]	P=0.032	–	P=0.107
Female			
Nephropathy			
Overall rates	21/49 (43%)	43/50 (86%)	42/50 (84%)
Severity grade			
None	28	7	8
Minimal	19	35	22
Mild	2	8	20
Moderate	0	0	0
Marked	0	0	0
Average severity grade	0.47	1.02**	1.24**

** Significantly different (P≤0.001) from the control group by the Mann-Whitney U test
[a] Number of lesion-bearing animals/number of animals examined microscopically
[b] Severity grade: none=0; minimal=1; mild=2; moderate=3; marked=4.
[c] 2-year historical incidence for vehicle control groups in NTP water gavage studies: 0/205
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the "Vehicle Control" column 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 test regards these lesions as nonfatal.
[g] Not applicable; no neoplasms in animal group

Nasal Cavity: An increased incidence of inflammatory lesions was observed in dosed mice (males: vehicle control, 1/50; 5 mg/kg, 4/50; 10 mg/kg, 16/50; females: 2/50, 4/50, 14/50; Tables C5 and D4). These lesions primarily consisted of an infiltration of granulocytes in the nasal mucosa, but in some animals, focal aggregates of lymphocytes were also present. Additionally, metaplasia of the nasal mucosa occurred and consisted of a transition from a metaplasia of the olfactory epithelium to a respiratory type of epithelium. This metaplastic change was dose related and appeared slightly more severe in the female mice (males: 3/50, 8/50, 41/50; females: 1/50, 20/50, 46/50).

Forestomach: While inflammation of the forestomach occurred in the 16-day studies, there was no evidence of treatment-related forestomach inflammation at the 15-month interim evaluations. In the 2-year studies, squamous cell hyperplasia was found in three high-dose males, and a squamous cell papilloma was found in another (Tables C1 and C5). A squamous cell carcinoma was found in a low-dose male mouse. Squamous cell hyperplasia was observed in two low-dose and three high-dose female mice (Table D4). There were also squamous cell papillomas of the forestomach in two high-dose females (Table D1). A squamous cell carcinoma was found in one control and one high-dose female. A few inflammatory and ulcerative lesions of the forestomach were seen in other mice but were not considered treatment related. The low incidences of forestomach papillomas in dosed mice were not considered chemical related.

GENETIC TOXICOLOGY

Mercuric chloride was negative in gene mutation tests with *Salmonella typhimurium* and *Drosophila melanogaster*, but positive in tests for genetic effects in mammalian cells *in vitro*. Mercuric chloride (0.003 to 33 μg/plate) was negative for induction of gene mutations in *S. typhimurium* (strains TA98, TA100, TA1535, and TA1537) when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Zeiger *et al.*, 1987; Table E1).

When tested without the addition of S9 activation enzymes in the mouse lymphoma assay, mercuric chloride was positive for induction of trifluorothymidine resistance in L5178Y cells. Significant increases in mutant colonies were observed in each of three trials conducted (McGregor *et al.*, 1988; Table E2). The loss of replicate positive control cultures (Trials 2 and 3) did not invalidate the responses observed with the treated cultures.

Mercuric chloride was negative for induction of sister chromatid exchanges in Chinese hamster ovary cells in the absence of S9 activation, but a weakly positive response was obtained in this assay when mercuric chloride was tested in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E3). In each of two trials with S9, a significant increase (>20%) in sister chromatid exchanges was noted only at the highest nonlethal dose tested (8.0 and 8.9 μg/mL, respectively). Mercuric chloride also induced chromosomal aberrations in Chinese hamster ovary cells, but the positive responses in this assay occurred in the absence, not the presence, of S9 (Table E4). In the first trial without S9, an increase in chromosomal aberrations occurred only at the highest concentration of mercuric chloride (7.95 μg/mL); in the second trial, significant increases in chromosomal aberrations occurred at all concentrations tested (6.03 to 8.04 μg/mL). Harvest time was extended in this second trial without S9 to offset the cell cycle delay produced by mercuric chloride treatment. Many of the cells which exhibited chromosomal damage following exposure to mercuric chloride contained complex aberrations (rearrangements and translocations) and, therefore, the total number of aberrations observed exceeds the number of cells damaged. The induction of a high number of complex chromosomal aberrations implicates mercuric chloride as a major cause of damage, as opposed to cytotoxicity, which would be expected to produce mainly simple breaks.

Mercuric chloride did not induce sex-linked recessive lethal mutations in germ cells of adult male *D. melanogaster* when administered in feed (363 ppm) or by injection (360 and 450 ppm; Table E5).

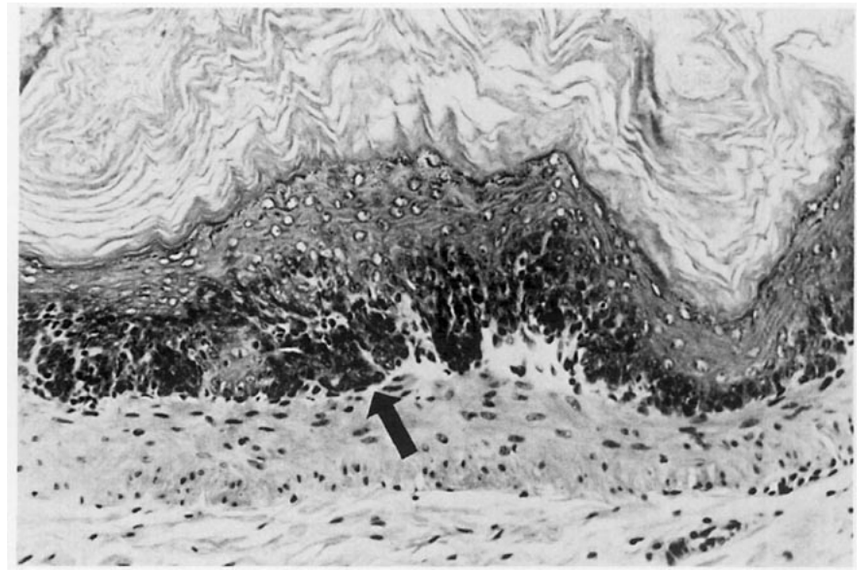

PLATE 1
Forestomach: Hyperplasia of the basal layer (arrow) and excess keratin on the surface of the forestomach epithelium of a male F344/N rat administered 5 mg/kg mercuric chloride by gavage for 2 years. 60×.

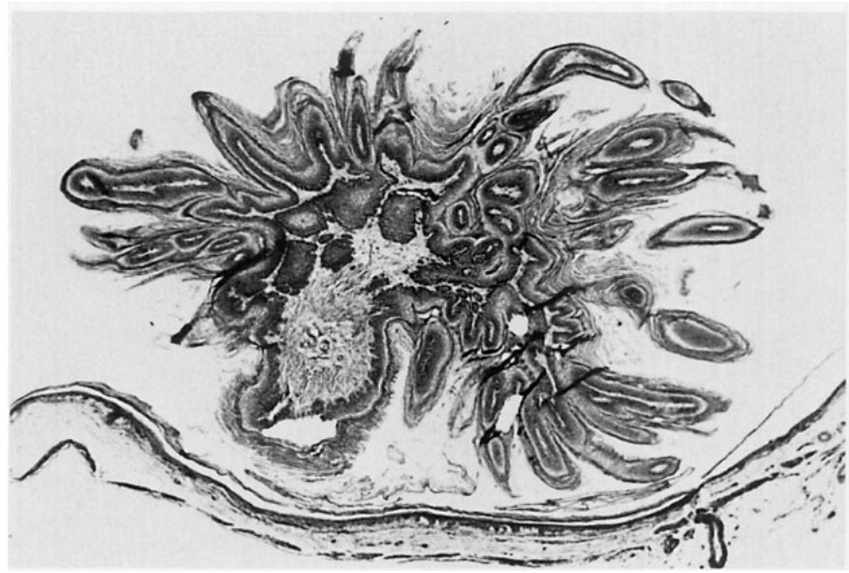

PLATE 2
Forestomach: Squamous cell papilloma in the forestomach of a male F344/N rat administered 5 mg/kg mercuric chloride by gavage for 2 years. 24×.

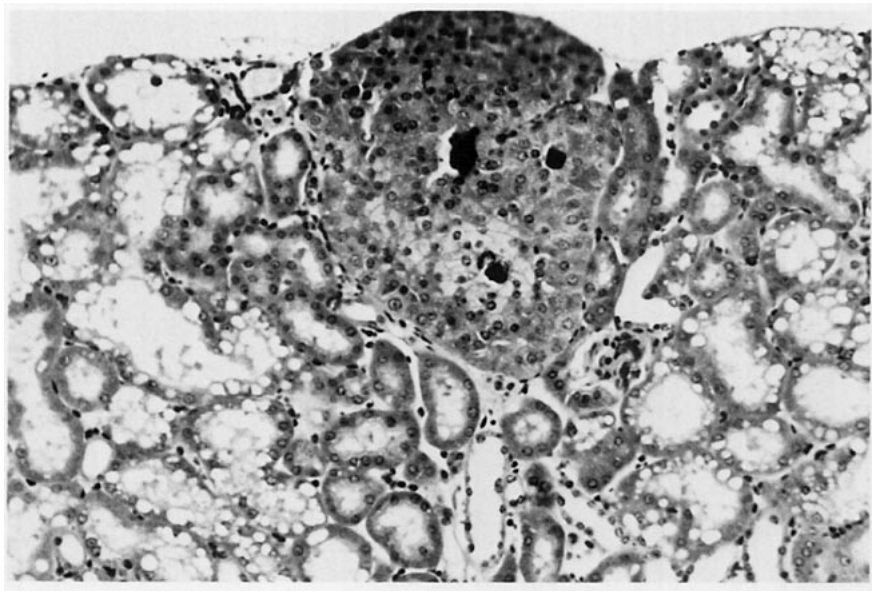

PLATE 3
Kidney: Renal tubule cell adenoma in a male $B6C3F_1$ mouse administered 10 mg/kg mercuric chloride by gavage for 2 years. 150×.

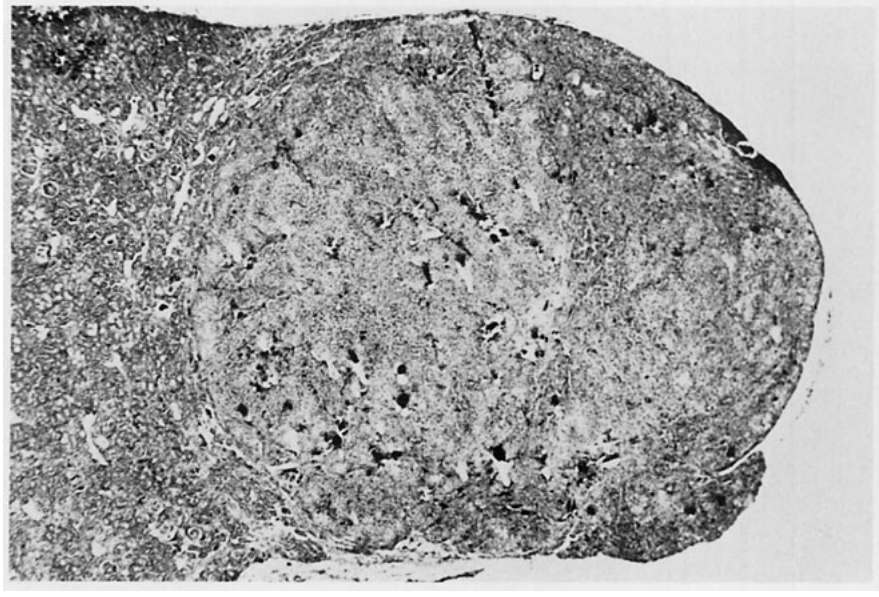

PLATE 4
Kidney: Renal tubule cell adenocarcinoma in a male $B6C3F_1$ mouse administered 10 mg/kg mercuric chloride by gavage for 2 years. 21×.

DISCUSSION AND CONCLUSIONS

The toxicity of mercury depends on its chemical form. Various mercury species and compounds have different toxicities depending on physical and chemical properties which affect absorption, distribution, tissue affinities, and stability within the human body. Elemental mercury in the liquid state has unique toxic effects that differ from those of mercury vapor; likewise, organic forms of mercury differ in toxicity from inorganic forms.

While mercuric chloride has been widely studied as a model of nephrotoxicity in a variety of animal species, there are no adequate long-term toxicity and carcinogenicity studies. Therefore, the National Toxicology Program (NTP) conducted 2-year studies of mercuric chloride administered by water gavage to F344 rats and B6C3F$_1$ mice. In order to determine doses for the 2-year studies, 16-day and 6-month studies were conducted to establish the level and range of mercury toxicities for these strains of rodents and to determine mercury concentrations in kidney, liver, and brain tissues following exposure.

The tissue concentrations of mercury in rats and mice exposed to mercuric chloride for 16 days and for 2, 4, and 6 months were highest in the kidney and lowest in the brain (Appendix I). In the 6-month rat studies, the mercury concentration in the kidneys of low-dose rats (0.312 mg/kg) increased with time (Table I2), which can be explained by the long half-life of mercury. In the high-dose group (5 mg/kg), mercury concentrations in the kidney were similar at 2, 4, and 6 months, indicating that a steady state had been reached. Although this was not expected based on the long half-life, it may be explained by the combined effect of enhanced absorption and accelerated excretion. Absorption was enhanced due to the corrosive effects of mercuric chloride on the gastrointestinal membrane; excretion was accelerated due to kidney malfunction. Mercury levels in the brain were less than 1% of those in the kidney. The range of mercury levels (87 to 123 ppm) in the kidneys of rats that received 5 mg/kg for 6 months was similar to the range (87 to 112 ppm) in mice that received 20 mg/kg. Mercury levels in the kidneys of mice that received 5 mg/kg mercuric chloride for 2, 4, or 6 months ranged between 27 ppm and 41 ppm. Thus, rats accumulated three times the mercury in their kidneys as did mice given a similar dose. In the mouse, the metabolic elimination rate for most chemicals is much faster than in the rat. Hence, the half-life of mercury in mice would be expected to be much shorter than in rats. This means that the accumulation of mercury in mice should not be as extensive as in rats, which was confirmed in the 6-month studies by the much lower mouse tissue concentrations of mercury. Other evidence for the faster metabolic elimination rate in mice was that there were no apparent differences in kidney mercury concentrations between 2, 4, and 6 months exposure in any dose group, indicating that a steady state had been reached which was independent of the dose. This may explain why kidney damage in mice was less severe than in rats, although both species received the same dose levels. No differences were seen in mercury levels between males and females; in contrast, Nielsen and Anderson (1990) have suggested that male mice may concentrate more mercury in the kidneys than do females.

Acute renal lesions in rats and mice were the result of high mercury concentrations in the kidney. These lesions were similar to those previously described in studies where mercuric chloride exposure had been used to study nephrotoxicity. Acute exposure to mercuric chloride caused necrosis of the renal tubule epithelium, specifically the proximal tubule epithelium. In rats examined 3 days after a single injection of mercuric chloride, necrosis was limited to the terminal pars recta, which is the straight portion of the proximal tubule (Biber *et al.*, 1968). The epithelium in the distal convoluted portion and toward the loop of Henle appeared normal. Cell debris, however, was present in the renal tubule lumen beyond the area of necrosis. In the same study, blood urea nitrogen levels and renal plasma flow were increased, but glomerular clearance was decreased, which led to decreased renal tubule absorption. Altered renal blood flow may contribute to the pathogenesis of mercuric chloride-induced nephropathy. However, Conger and Falk (1986) suggested that renal blood flow and distribution are

not altered immediately following mercuric chloride exposure and, thus, are not major pathogenic mechanisms of mercuric chloride-induced renal disease. In mice exposed to mercuric chloride, mercury was found in the glomerular filtrate and was absorbed by renal tubule epithelial cells through absorptive endocytosis (Hultman *et al.*, 1985). The acute nephropathy seen in the 16-day mice studies described in this report was similar to that reported in the literature.

Although the acute renal toxicity of mercuric chloride has been well documented, there have been few studies of the renal effects of long-term exposure. In the present 2-year studies, one of the principal toxic effects associated with the administration of a maximum tolerated dose of mercuric chloride occurred in the kidneys of male rats. The chronic nephrotoxicity of mercuric chloride was manifested as an increase in the severity of the spontaneous, progressive, degenerative lesions commonly seen in the kidneys of aging rats. In contrast, no observable effect in the kidneys of female rats could be attributed to mercuric chloride administration.

Male rats are more susceptible to nephrotoxicity than are females. The cumulative effects of mercuric chloride may exacerbate the age-related, spontaneous degenerative changes that typically are more severe in the kidneys of male rats. Aging of rats is associated with changes in glomerular permeability resulting in proteinuria, progressive glomerulosclerosis, tubule damage, inflammation, and interstitial fibrosis. It is unknown if the tubule damage is entirely secondary to the changes in the glomeruli or is the direct effect of factors still not identified. The precise causes of this disease are unknown, although dietary factors such as protein intake are known to influence the progression and severity of the renal lesions. One factor which may contribute in part to the greater severity of tubule damage in males is the low molecular weight protein $\alpha_{2\mu}$-globulin, which is filtered by the kidney at the rate of 50 to 60 mg/day in normal young adult males (Neuhaus *et al.*, 1981). In contrast, females excrete less than 1% of the $\alpha_{2\mu}$-globulin excreted by male rats (Vandoren *et al.*, 1983). In males, approximately 60% of the $\alpha_{2\mu}$-globulin is reabsorbed by epithelial cells of the proximal convoluted tubule, primarily the P_2 segment, where it is slowly or poorly hydrolyzed in lysosomes (Charbonneau *et al.*, 1988). Cells containing the protein undergo degeneration as well as necrosis, and a higher rate of cell turnover is observed in the P_2 segment compared with other segments of the proximal convoluted tubule (Short *et al.*, 1987). Thus, $\alpha_{2\mu}$-globulin may play a role in spontaneous nephropathy and contribute to the increased severity of the disease in males.

Muraoka and Itoh (1980) have proposed that the greater susceptibility of the male rat to the acute toxic effects of mercuric chloride may be due to the greater number of sulfhydryl groups in the kidneys of males compared to females. Mercury ions have an affinity for the sulfhydryl groups of active sites in some enzymes, thus affecting the function of a number of different proteins and enzyme systems such as pyruvate kinase (Dieter *et al.*, 1983). A fewer number of sulfhydryl groups may protect vital components of the cell, such as coenzyme A, from the effects of mercuric chloride (Sharma, 1987).

The increased incidence of parathyroid hyperplasia and fibrous osteodystrophy in male rats receiving mercuric chloride indicates that the extent of nephropathy in dosed males was severe enough to compromise renal function. Hyperparathyroidism frequently accompanies severe nephropathy in rats. The progressive loss of renal function disrupts calcium and phosphorus homeostasis, leading to prolonged stimulation of the parathyroid gland and resulting in hyperplasia and elevated levels of parathyroid hormone. Fibrous osteodystrophy is the result of the disruption in calcium/phosphorus homeostasis, the effects of parathyroid hormone, and reduced conversion of the active form of vitamin D in the kidney. The reduced survival in male rats receiving mercuric chloride is likely due, in part, to the compound-related increased severity of renal disease as demonstrated in several other NTP 2-year studies.

Mercuric chloride also produced an increased incidence of nephropathy in dosed male and female mice in the 2-year studies. In the high-dose groups, kidney lesions in males were more severe than in females. Mice had a lower incidence and lesser severity of nephropathy than did rats, which may have been due to a combination of less severe spontaneous nephropathy and lower kidney mercury concentrations. Based on analysis of mercury in tissues from animals in the 6-month studies, mice were expected to have lower kidney mercury levels than rats.

In addition to the chemical-related increased severity of nephropathy in male rats, there was a slight increase in the incidence of hyperplasia of the renal tubules in high-dose rats (males: 1/50, 1/50, 4/50; females: 0/50, 0/50, 2/50). In the initial evaluation, a small number of renal tubule neoplasms, primarily adenomas, also occurred in dosed rats; no renal neoplasms were observed in the controls (males: 0/50, 2/50, 0/50; females: 0/50, 0/49, 1/50).

In the 2-year mouse studies, renal tubule adenomas were observed in two high-dose males and an adenocarcinoma was found in a third. Although the incidence of renal neoplasms in the high-dose male group was not significantly greater than that of controls, the rare occurrence of these neoplasms in untreated historical control male mice led to the conclusion that the neoplasms might be chemical related. There was no increased incidence of renal tubule hyperplasia in dosed male mice.

Because of the slight increased incidence of hyperplasia in high-dose rats, and the occurrence of several renal neoplasms in high-dose male mice, the NTP prepared and examined additional sections from the formalin-fixed kidneys of rats and mice from the control and high-dose groups. The NTP and other investigators (Kurokawa *et al.*, 1985) have found that multiple sectioning of the kidney, rather than single sectioning, may allow more precise evaluations of the potential chemical-related induction of renal tubule neoplasms because the majority of renal neoplasms in these and other studies are microscopic and cannot be seen by macroscopic examination at necropsy.

Evaluation of the step sections prepared from the residual formalin-fixed kidneys identified focal hyperplasia in two control and eight high-dose male rats; adenomas were found in four control and five high-dose males. In female rats, hyperplasia was found in two control and three high-dose animals; an adenoma was observed in one high-dose female. Thus, the data derived from the step sections confirmed a slight chemical-related increase in the incidence of hyperplasia in male rats, but the number of adenomas in control and high-dose male and female groups was similar. Further, in a recent NTP study where kidney step sections were prepared, adenomas were found in five control male rats (NTP, 1990). The step sections also provided little support for a chemical-related increased incidence of renal neoplasms in female rats.

No additional renal neoplasms were found in the step sections prepared from the kidneys of male or female mice. Further, there was no overall increase in renal tubule hyperplasia in dosed male mice to support a carcinogenic effect. Thus, the small number of renal neoplasms in male mice is considered as equivocal evidence of carcinogenicity.

In contrast, additional lesions found by the step-section procedure in studies of 2,4-diaminophenol dihydrochloride resulted in a call of some evidence for male mice. Single-section results would not have supported this call (NTP, 1992).

The renal neoplasms found in mice were unexpected. Chemical-related toxicity was less severe in male mice than in the rats, and in the 6-month studies, mercury concentrations in the kidneys of male rats receiving 5 mg/kg were 87 to 95 ppm while mercury concentrations in the kidneys of male mice receiving 5 mg/kg were 27 to 37 ppm. In the 6-month studies, mercury concentrations in the kidneys of mice receiving 20 mg/kg were similar to those of rats receiving 5 mg/kg. Historically, in the NTP program, male rats are more likely to have kidney neoplasms than are female rats or mice of either sex. The kidney is not a common site for carcinogenesis in mice. Male mice have had increased incidences of renal tubule neoplasms in only four of the nearly 400 completed NTP studies. The four chemicals shown to induce renal tubule neoplasms in mice are nitrilotriacetic acid (NCI, 1977), tris (2,3-dibromopropyl) phosphate (NCI, 1978), 2,4-diaminophenol dihydrochloride (NTP, 1992), and bromodichloromethane (NTP, 1987).

When administered by gavage, mercuric chloride is known to be directly cytotoxic and to cause acute toxic changes in the gastric mucosa. In the 16-day mouse studies, high doses of mercuric chloride (up to 80 mg/kg) were associated with acute gastritis; similar lesions were not seen in rats. The gastric effects may be related to the concentration of the mercury in contact with the gastric mucosa following gavage. Mercury concentrations in the gavage doses administered to rats ranged from 0.125 to 2.0 mg/mL compared to 0.5 to 8.0 mg/mL for mice.

In addition to the acute gastric effects of mercuric chloride, basal cell hyperplasia (diagnosed as acanthosis) of the forestomach was observed in dosed rats after 15 months of administration and increased in

severity after 2 years. Moreover, the administration of mercuric chloride produced focal papillary hyperplasia and squamous cell papillomas of the forestomach. In six of the 12 high-dose male rats with squamous cell papillomas, multiple papillomas were identified; squamous cell carcinomas did not develop. It is not known if the squamous cell papillomas had the potential to progress to carcinomas, and there was no evidence that the papillomas were proceeding to malignancy. Thus, for male rats, there was some evidence, rather than clear evidence, of carcinogenic activity related to administration of mercuric chloride.

In female rats, the incidence of forestomach hyperplasia was increased in the high-dose group, and squamous cell papillomas developed in two high-dose females. Forestomach squamous cell papillomas are uncommon in female rats and have not occurred in 265 untreated historical controls. Since mercuric chloride was administered by gavage, the concentration of mercury in the forestomach mucosa was expected to be high. The infrequent occurrence of squamous cell papillomas in historical control females, the chemical-related increased incidence of forestomach hyperplasia, and similar occurrences in male rats support an association between the forestomach squamous cell papillomas and the administration of mercuric chloride. Because only two squamous cell papillomas were found, the data were considered to represent equivocal evidence of carcinogenic activity in female rats.

In the 6-month and 2-year studies, mice showed little evidence of mercuric chloride toxicity affecting the forestomach; one high-dose male had a squamous cell papilloma and one low-dose male had a squamous cell carcinoma of the forestomach. Squamous cell carcinomas were present in one control and one high-dose female, and two squamous cell papillomas were found in high-dose female mice. Only eight forestomach hyperplasias were found in mice: three in high-dose males, three in high-dose females, and two in low-dose females. The incidence of forestomach neoplasms in dosed male and female mice were within the range of historical controls and could not be regarded as evidence of carcinogenic activity related to the administration of mercuric chloride.

The nasal mucosa was not expected to have lesions associated with mercuric chloride exposure; however, after 15 months, the incidence of inflammatory lesions of the nasal mucosa was increased in high-dose mice. A dose-related increase in inflammation with respiratory-type metaplasia of olfactory epithelium was found in more than 80% of the high-dose mice examined after 2 years. These changes were found in rats at 2 years, but not at 15 months. The pathogenesis of this lesion is not known, but several explanations might account for its presence. Volatile substances given by gavage are sometimes exhaled, causing upper respiratory lesions. During gavage a small portion of the dose may be deposited in the oral pharynx, and thus would come in direct contact with the nasal mucosa, but this method could not explain the uniformly high rate of olfactory epithelial metaplasia. Although mercuric chloride given by gavage would not result in the release of mercury vapors, circulating mercuric chloride may have some affinity for nasal tissues. Since mercury has been shown to have a special affinity for ectodermal and endodermal epithelial cells and glands (Berlin, 1986), an increase in tissue affinity for mercury might be the most suitable explanation for the pathogenesis of metaplasia.

The incidence of thyroid follicular cell hyperplasia in rats was similar for control and high-dose groups. In male rats, follicular cell adenomas occurred in one control male and in four low-dose males, but not in high-dose males; however, six follicular cell carcinomas were found in high-dose males. Although induced follicular cell carcinomas usually result from increased incidences of hyperplasia and follicular cell adenomas, the incidences of hyperplasia and adenomas found in high-dose male rats were not increased. Further, chemicals that induce thyroid follicular cell neoplasms in male rats will often induce neoplasms in female rats or mice, but there was no supporting evidence for neoplastic activity in the thyroid for any group in these studies other than male rats. Thus, it is difficult to associate the thyroid neoplasms with the administration of mercuric chloride. The overall historical incidence of follicular cell carcinomas in untreated male controls is 1/259 (0.4%). The increased incidence of thyroid follicular cell carcinomas in the male rats may have been related to the administration of mercuric chloride.

These studies were considered adequate to assess the potential carcinogenicity of mercuric chloride. Mercuric chloride was given at levels that caused toxicity, and the 6-month studies suggest that the animals could not have tolerated higher exposures.

The majority of male rats (greater than 50% in all groups) survived to 90 weeks, but there was high mortality during the last 15 weeks of the study due to severe renal disease. The toxicity of mercuric chloride in the kidney clearly limited the detection of potential carcinogenicity in male rats. This suggests that the potential toxicity of mercuric chloride may pose a greater hazard than its potential carcinogenicity. Survival of dosed female rats and dosed mice was 60% or greater throughout the studies.

In the NTP genetic toxicity studies, mercuric chloride was negative for induction of gene mutations in four strains of *Salmonella typhimurium*, and was negative for sister chromatid exchanges in Chinese hamster ovary cells in the absence of S9 but weakly positive with S9. Mercuric chloride induced chromosomal aberrations in Chinese hamster ovary cells without S9 but not in the presence of S9. Many of the damaged cells contained complex and multiple aberrations; cell cycle delay and a significant reduction in cell confluence were indications of the toxicity of mercuric chloride at the doses tested. Thus, the toxicity of mercuric chloride in this assay may be a factor to consider in the evaluation of these results (Bradley *et al.*, 1987; Galloway *et al.*, 1987), although it is unclear what role, if any, cytotoxicity plays in the induction of chromosomal aberrations *in vitro* (Scott *et al.*, 1991). Mercuric chloride has also been reported to induce chromosomal changes in cultured Chinese hamster ovary cells (Howard *et al.*, 1991), in the newt, *Pleurodeles waltl* (Zoll *et al.*, 1988), and in human lymphocytes (Verschaeve *et al.*, 1985). The studies in human lymphocytes showed that disassociation of acrocentric chromosomes occurred at lower concentrations than did clastogenic effects (Verschaeve *et al.*, 1985).

In the present studies, mercuric chloride was also positive in the mouse lymphoma assay but was negative for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*. This is in contrast to the studies of Sharma *et al.* (1989), where chromosomal aberrations and dominant lethal mutations were found in the mosquito, *Culex fatigans*. The difference between the study results in *D. melanogaster* and *Culex* are unexplained since the mosquitos were exposed to much lower concentrations of mercuric chloride than in these *D. melanogaster* studies. Cultured mouse embryos exposed to mercuric chloride and then transferred to pseudopregnant mice showed that mercuric chloride was embryotoxic (Katayama and Matsumoto, 1985).

The present studies and those in the literature indicate that mercuric chloride is genotoxic. Mercuric chloride may exert its effect by nonspecific protein binding, but selective binding and inactivation of the RNA polymerase I may also be another important mechanism of action for mercuric chloride (Verschaeve *et al.*, 1985). Despite the lack of mutagenic activity displayed by mercuric chloride in *S. typhimurium*, the chemical is clearly genotoxic *in vitro* by virtue of its clastogenic action in mammalian cell assays. These effects appear to be due to binding and subsequent inactivation of cellular proteins, particularly DNA maintenance enzymes.

This study also presented some information relative to the value of group housing versus individual housing of the male B6C3F$_1$ mice. Initially, the male mice were group housed, but during the course of the study a program-wide decision was made to individually house male mice due to problems with aggression in this strain. During the first 7 months of group housing, 22 males died from secondary complications due to bite wounds, while in the 7 months following separation only three additional male mice died.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of mercuric chloride in male F344 rats based on the increased incidence of squamous cell papillomas of the forestomach. Marginally increased incidences of thyroid follicular cell adenomas and carcinomas may have been related to mercuric chloride exposure. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in female F344 rats based on two squamous cell papillomas of the forestomach. There was *equivocal evidence of carcinogenic activity* of mercuric chloride in male B6C3F$_1$ mice based on the occurrences of two renal tubule adenomas and one renal tubule adenocarcinoma. There was *no evidence of carcinogenic activity* of mercuric chloride in female B6C3F$_1$ mice receiving 5 or 10 mg/kg.

Nonneoplastic lesions associated with exposure to mercuric chloride included increased severity of nephropathy in male rats and male and female mice. There was an increased incidence of renal tubule hyperplasia in male rats. The incidence of

forestomach hyperplasia was increased in dosed male and female rats. Increased incidences of nasal mucosa inflammation were associated with mercuric chloride administration in rats. Increased incidences of olfactory epithelial metaplasia in mice were also associated with mercuric chloride administration.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of peer review comments and the public discussion on this Technical Report appears on page 11.

REFERENCES

Andersen, O. (1983). Effects of coal combustion products and metal compounds on sister chromatid exchange (SCE) in a macrophagelike cell line. *Environ. Health Perspect.* **47**, 239-253.

Andren, A.W., and Nriagu, J.O. (1979). The global cycle of mercury. In *The Biogeochemistry of Mercury in the Environment* (J.O. Nriagu, Ed.), pp. 1-21. Elsevier/North-Holland, Amsterdam.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Aten, J., Bosman, C.B., Rozing, J., Stijnen, T., Hoedemaeker, P.J., and Weening, J.J. (1988). Mercuric chloride-induced autoimmunity in the Brown Norway rat. *Am. J. Pathol.* **133**, 127-138.

Barnes, J.L., McDowell, E.M., McNeil, J.S., Flamenbaum, W., and Trump, B.F. (1980). Studies on the pathophysiology of acute renal failure. V. Effect of chronic saline loading on the progression of proximal tubular injury and functional impairment following administration of mercuric chloride in the rat. *Virchows Arch. [B]* **32**, 233-260.

Benes, P., and Havlik, B. (1979). Speciation of mercury in natural waters. In *The Biogeochemistry of Mercury in the Environment* (J.O. Nriagu, Ed.), pp. 175-202. Elsevier/North-Holland, Amsterdam.

Berlin, M. (1986). Mercury. In *Handbook on the Toxicology of Metals* (L. Friberg, G.F. Nordberg, V.B. Vouk, and E. Kessler, Eds.), 2nd ed. Vol. II: Specific metals, pp. 387-445. Elsevier/North Holland, Amsterdam.

Biber, T.U.L., Mylle, M., Baines, A.D., Gottschalk, C.W., Oliver, J.R., and MacDowell, M.C. (1968). A study by micropuncture and microdissection of acute renal damage in rats. *Am. J. Med.* **44**, 664-705.

Bradley, M.O., Taylor, V.I., Armstrong, M.J., and Galloway, S.M. (1987). Relationships among cytotoxicity, lysosomal breakdown, chromosome aberrations, and DNA double-strand breaks. *Mutat. Res.* **189**, 69-79.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Burkart, W., and Ogorek, B. (1986). Genotoxic action of cadmium and mercury in cell cultures and modulation of radiation effects. *Toxicol. Environ. Chem.* **12**, 173-183.

Cantoni, O., and Costa, M. (1984). Analysis of the induction of alkali sensitive sites in the DNA by chromate and other agents that induce single strand breaks. *Carcinogenesis* **5**, 1207-1209.

Cantoni, O., Evans, R.M., and Costa, M. (1982). Similarity in the acute cytotoxic response of mammalian cells to mercury(II) and X-rays: DNA damage and glutathione depletion. *Biochem. Biophys. Res. Commun.* **108**, 614-619.

Cantoni, O., Sestili, P., and Cattabeni, F. (1986). Regulatory role of extracellular medium components in metal induced cyto- and geno-toxicity. *Bull. Environ. Contam. Toxicol.* **37**, 883-889.

Charbonneau, M., Strasser, J., Borghoff, S.J., and Swenberg, J.A. (1988). *In vitro* hydrolysis of ^{14}C-$\alpha_{2\mu}$-globulin isolated from male rat kidney. *Toxicologist* **8**, 135.

Christie, N.T., Cantoni, O., Evans, R.M., Meyn, R.E., and Costa, M. (1984). Use of mammalian DNA repair-deficient mutants to assess the effects of toxic metal compounds on DNA. *Biochem. Pharmacol.* **33**, 1661-1670.

Code of Federal Regulations (CFR), **21**, part 58.

Conger, J.D., and Falk, S.A. (1986). Glomerular and tubular dynamics in mercuric chloride-induced acute renal failure. *J. Lab. Clin. Med.* **107**, 281-289.

Cox, D.R. (1972). Regression models and life tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology* (W.G. Flamm and R.J. Lorentzen, Eds.), pp. 13-59, Princeton Scientific, Princeton, NJ.

Dash, S., Panda, K.K., and Panda, B.B. (1988). Biomonitoring of low levels of mercurial derivatives in water and soil by *Allium* micronucleus assay. *Mutat. Res.* **203**, 11-21.

Dieter, M.P., Luster, M.I., Boorman, G.A., Jameson, C.W., Dean, J.H., and Cox, J.W. (1983). Immunological and biochemical responses in mice treated with mercuric chloride. *Toxicol. Appl. Pharmacol.* **68**, 218-228.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumor prevalence data. *Appl. Statist.* **32**, 236-248.

Dreisbach, R.H. (1980). *Handbook of Poisoning: Prevention, Diagnosis and Treatment.* Lange Medical Publications, Los Altos, CA.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1095-1121.

Fawkes, J., Folsom, M., and Oswald, E.O. (1976). The determination of total mercury in biological tissues by a modified potassium permanganate procedure. *Anal. Chim. Acta* **82**(1), 54-65.

Fukunaga, M., Kurachi, Y., and Mizuguchi, Y. (1982). Action of some metal ions on yeast chromosomes. *Chem. Pharm. Bull.* **30**, 3017-3019.

Galloway, S.M., Bloom, A.D., Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985). Development of a standard protocol for *in vitro* cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. *Environ. Mutagen.* **7**, 1-51.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Ganote, C.E., Reimer, K.A., and Jennings, R.B. (1974). Acute mercuric chloride nephrotoxicity: An electron microscopic and metabolic study. *Lab. Invest.* **31**, 633-647.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *J. Natl. Cancer Inst.* **62**, 957-974.

Gosselin, R.E., Hodge, H.C., Smith, R.P., and Gleason, M.N. (1984). *Clinical Toxicology of Commercial Products: Acute Poisoning*, 5th ed. Williams and Wilkins, Baltimore, MD.

Hamilton-Koch, W., Snyder, R.D., and Lavelle, J.M. (1986). Metal-induced DNA damage and repair in human diploid fibroblasts and Chinese hamster ovary cells. *Chem-Biol. Interact.* **59**, 17-28.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J., Rao, G.N., Arnold, J., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *J. Natl.Cancer Inst.* **75**, 975-984.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Howard, W., Leonard, B., Moody, W., and Kochhar, T.S. (1991). Induction of chromosome changes by metal compounds in cultured CHO cells. *Toxicol. Lett.* **56**, 179-186.

Hultman, P., Enestrom, S., and von Schenck, H. (1985). Renal handling of inorganic mercury in mice. The early excretion phase following a single intravenous injection of mercuric chloride studied by the silver amplification method. *Virchows Arch.* [B] **49**, 209-224.

International Programme on Chemical Safety (IPCS) (1989). Environmental Health Criteria 86, Mercury-Environmental Aspects, World Health Organization, 1989, pp 1-115.

Janicki, K., Dobrowolski, J., and Drasnicki, K. (1987). Correlation between contamination of the rural environment with mercury and the occurrence of leukemia in men and cattle. *Chemosphere* **16**, 253-257.

Jennette, K.W., Lippard, S.J., and Ucko, D.A. (1975). ^{13}C magnetic resonance investigation of mercury (II) binding to nucleosides and thiolated nucleosides in dimethyl sulfoxide. *Biochim. Biophys. Acta* **402**, 403-412.

Jonckheere, A. (1954). A distribution-free k-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Kada, T., Tutikawa, K., and Sadaie, Y. (1972). *In vitro* and host-mediated 'rec-assay' procedures for screening chemical mutagens; and phloxine, a mutagenic red dye detected. *Mutat. Res.* **16**, 165-174.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Katayama, S., and Matsumoto, N. (1985). Toxic effects of chemicals on mouse post-blastocyst development--a trial to establish a testing system for embryotoxicity. *Nippon Sanka Fujinka Gakkai Zasshi* **37** (Suppl. 3), 421-430.

Kurokawa, K., Matsushima, M., Imazawa, T., Takamura, N., Takahashi, M., and Hayashi, Y. (1985). Promoting effect of metal compounds on rat renal tumorigenesis. *J. Am. Coll. Toxicol.* **4**, 321-330.

Leonard, A., Jacquet, P., and Lauwerys, R.R. (1983). Mutagenicity and teratogenicity of mercury compounds. *Mutat. Res.* **114**, 1-18.

Magos, L. (1987). Mercury. In *Handbook on the Toxicity of Inorganic Compounds* (H.G. Seiler and H. Sigel, Eds.), pp 419-436. Marcel Dekker, Inc., New York.

Margolin, B., Collings, B., and Mason, J. (1983). Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. *Environ. Mutagen.* **5**, 705-710.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

Marzin, D.R., and Phi, H.V. (1985). Study of the mutagenicity of metal derivatives with *Salmonella typhimurium* TA102. *Mutat. Res.* **155**, 49-51.

Matsui, S. (1980). Evaluation of a *Bacillus subtilis* 'rec-assay' for the detection of mutagens which may occur in water environments. *Weed Res.* **14**, 1613-1620.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J. Natl. Cancer Inst.* **76**, 283-289.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C., and Caspary, W.J. (1988). Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay. III. 72 coded chemicals. *Environ. Mol. Mutagen.* **12**, 85-154.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

The Merck Index (1976). 9th ed. (M. Windholz, Ed.). Merck and Company, Rahway, NJ.

The Merck Index. (1983). 10th ed. (M. Windholz, Ed.). Merck and Company, Rahway, NJ.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-628, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Montaldi, A., Zentilin, L., Venier, P., Gola, I., Bianchi, V., Paglialunga, S., and Levis, A.G. (1985). Interaction of nitrilotriacetic acid with heavy metals in the induction of sister chromatid exchanges in cultured mammalian cells. *Environ. Mutagen.* **7**, 381-390.

Morimoto, K., Iijima, S., and Koizumi, A. (1982). Selenite prevents the induction of sister chromatid exchanges by methyl mercury and mercuric chloride in human whole-blood cultures. *Mutat. Res.* **102**, 183-192.

Muraoka, Y., and Itoh, F. (1980). Sex difference of mercuric chloride-induced renal tubular necrosis in rats--from the aspect of sex differences in renal mercury concentration and sulfhydryl levels. *J. Toxicol. Sci.* **5**, 203-214.

Myhr, B.C., Bower, L., and Caspary, W. (1985). Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. *Prog. Mutat. Res.* **5**, 555-568.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1977). Bioassays of Nitrilotriacetic Acid (NTA) and Nitrilotriacetic Acid, Trisodium Salt, Monohydrate ($Na_3NTA \cdot H_2O$) for Possible Carcinogenicity (CAS No. 139-13-9 (NTA), CAS No. 18662-53-8 ($Na_3NTA \cdot H_2O$)). Technical Report Series No. 6. NIH Publication No. 77-806. U.S Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1978). Bioassay of Tris (2,3-Dibromopropyl) Phosphate for Possible Carcinogenicity. Technical Report Series No. 76. NIH Publication No. 78-1326. U.S Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH) (1990). National Occupational Exposure Survey (NOES) (1981-1983), unpublished provisional data as of July 1, 1990.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1987). Toxicology and Carcinogenesis Studies of Bromodichloromethane (CAS No. 75-27-4) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 321. NIH Publication No. 88-2537. U.S Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1990). Toxicology and Carcinogenesis Studies of Toluene (CAS No. 108-88-3) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). Technical Report Series No. 371. NIH Publication No. 90-2826. U.S Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1992). Toxicology and Carcinogenesis Studies of 2,4-Diaminophenol Dihydrochloride (CAS No. 137-09-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 401. NIH Publication No. 92-2856. U.S Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Neuhaus, O.W., Flory, W., Biswas, N., and Hollerman, C.E. (1981). Urinary excretion of $\alpha_{2\mu}$-globulin and albumin by adult male rats following treatment with nephrotoxic agents. *Nephron* **28**, 133-140.

Nielsen, J.B., and Andersen, O. (1990). Disposition and retention of mercuric chloride in mice after oral and parental administration. *J. Toxicol. Environ. Health* **30**, 167-180.

Nishioka, H. (1975). Mutagenic activities of metal compounds in bacteria. *Mutat. Res.* **31**, 185-189.

Oberly, T.J., Piper, C.E., and McDonald, D.S. (1982). Mutagenicity of metal salts in the L5178Y mouse lymphoma assay. *J. Toxicol. Environ. Health* **9**, 367-376.

Phillips, R., Yamauchi, M., Cote, M.G., and Plaa, G.L. (1977). Assessment of mercuric chloride-induced nephrotoxicity of *p*-aminohippuric acid uptake and the activity of four gluconeogenic enzymes in rat renal cortex. *Toxicol. Appl. Pharmacol.* **41**, 407-422.

Ramel, C. (1969). Genetic effects of organic mercury compounds. I. Cytological investigations on *Allium* roots. *Hereditas* **61**, 208-233.

Ramel, C. (1972). Genetic effects. In *Mercury in the Environment: Toxicological Effects and Epidemiological and Toxicological Appraisal.* (L. Friberg and D. Vostal, Eds.), pp. 169-181. CRC Press, Cleveland, OH.

Robison, S.H., Cantoni, O., and Costa, M. (1982). Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. *Carcinogenesis* **3**, 657-662.

Rothstein, A., and Hayes, A.D. (1960). The metabolism of mercury in the rat studied by isotope techniques. *J. Pharmacol. Exp. Ther.* **130**, 166-176.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia, PA.

Sapin, C., Druet, E., and Druet, P. (1977). Induction of anti-glomerular basement membrane antibodies in the Brown-Norway rat by mercuric chloride. *Clin. Exp. Immunol.* **28**, 173-179.

Scott, D., Galloway, S.M., Marshall, R.R., Ishidate, M., Jr., Brusick, D., Ashby, J., and Myhr, B.C. (1991). Genotoxicity under extreme culture conditions. A report from ICPEMC task group 9. *Mutat. Res.* **257**, 147-204.

Selypes, A., Nagymajtenyi, L., and Berencsi, G. (1983). Investigation of the mutagenic and embryotoxic effects on mice of exposure to mercury fumes. *MUNKA* **29**, 152-154.

Sharma, D.C. (1987). Biochemical basis of the toxicity of mercury. *Med. Hypotheses* **23**, 259-263.

Sharma, G.P., Sobti, R.C., Chaudhry, A., and Ahluwalia, K.K. (1988). Genotoxicity of two heavy metal compounds-lead acetate and mercuric chloride in the mosquito, *Anopheles stephensi liston* (*Culicidae: Diptera*). *Cytologia* **53**, 263-267.

Sharma, G.P., Sobti, R.C., Chaudhry, A., and Ahluwalia, K.K. (1989). Chromosome aberrations and dominant lethals in *Culex fatigans* due to mercuric chloride. *Cytobios* **59**, 131-135.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Short, B.G., Burnett, V.L., Cox, M.G., Bus, J.S., and Swenberg, J.A. (1987). Site-specific renal cytotoxicity and cell proliferation in male rats exposed to petroleum hydrocarbons. *Lab. Invest.* **57**, 564-577.

Siebert, D. (1981). Further improvement of a genetic prescreening test pattern for carcinogenic effects of environmental chemicals. In *Genetic Effects of Environmental Chemicals.* Comm. Eur. Communities, (Rep) Eur (12/1126/81-EN):12-15.

Sin, Y.M., Teh, W.F., Wong, M.K., and Reddy, P.H. (1990). Effect of mercury on glutathione and thyroid hormones. *Bull. Environ. Contam. Toxicol.* **44**, 616-622.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *J. Natl. Cancer Inst.* **67**, 233.

Suter, K.E. (1975). Studies on the dominant-lethal and fertility effects of the heavy metal compounds methylmercuric hydroxide, mercuric chloride, and cadmium chloride in male and female mice. *Mutat. Res.* **30**, 365-374.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. *Science* **236**, 933-941.

Valencia, R., Mason, J.M., and Zimmering, S. (1989). Chemical mutagenesis testing in *Drosophila*. VI. Interlaboratory comparison of mutagenicity tests after treatment of larvae. *Environ. Mol. Mutagen.* **14**, 238-244.

Vandoren, G., Mertens, B., Heyns, W., Van Baelen, H., Rambauts, W., and Verhoeven, G. (1983). Different forms of $\alpha_{2\mu}$-globulin in male and female rat urine. *Eur. J. Biochem.* **134**, 175-181.

Vasil'eva, I.M., Sdirkova, N.I., Zasukhina, G.D., Butenko, P.G., Krasovski, G.N., and Vasyukovich, L.Y. (1982). Determination of the mutagenic potential of one of the environmental pollutants-mercuric chloride. *Tsitol. Genet.* **16**, 21-24.

Verschaeve, L., Kirsch-Volders, M., Hens, L., and Susanne, C. (1978). Chromosome distribution studies in phenyl mercury acetate exposed subjects and in age-related controls. *Mutat. Res.* **57**, 335-347.

Verschaeve, L., Kirsch-Volders, M., Hens, L., and Susanne, C. (1985). Comparative *in vitro* cytogenetic studies in mercury-exposed human lymphocytes. *Mutat. Res.* **157**, 221-226.

Weast, R.C., Ed. (1982). *CRC Handbook of Chemistry and Physics*. 62nd ed. CRC Press, Boca Raton, FL.

World Health Organization (WHO) (1976). Environmental Health Criteria 1: Mercury. World Health Organization, Geneva.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Wong, P.K. (1988). Mutagenicity of heavy metals. *Bull. Environ. Contam. Toxicol.* **40**, 597-603.

Zasukhina, G.D., Vasil'eva, I.M., Sdirkova, N.I., Krasovski, G.N., Vasyokovich, L. Y., Kenesariev, U.I., and Butenko, P.G. (1983). Mutagenic effect of thallium and mercury salts on rodent cells with different repair activities. *Mutat. Res.* **124**, 163-173.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W. (1987). *Salmonella* mutagenicity tests. III. Results from the testing of 255 chemicals. *Environ. Mutagen.* **9** (Suppl. 9), 1-109.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zimmering, S., Mason, J.M., Valencia, R., and Woodruff, R.C. (1985). Chemical mutagenesis testing in *Drosophila*. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ. Mol. Mutagen.* **7**, 87-100.

Zoll, C., Saouter, E., Boudcu, A., Ribeyre, F., and Jaylet, A. (1988). Genotoxicity and bioaccumulation of methyl mercury and mercuric chloride *in vivo* in the newt *Pleurodeles waltl*. *Mutagenesis* **3**, 337-343.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF MERCURIC CHLORIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	2.5 mg/kg	5 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	20	19	32
Natural deaths	4	21	13
Survivors			
Terminal sacrifice	26	10	5
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(50)	(50)	(50)
Intestine small, duodenum	(50)	(49)	(50)
Intestine small, ileum	(49)	(50)	(49)
Intestine small, jejunum	(49)	(50)	(50)
Carcinoma	2 (4%)		
Liver	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hepatocellular carcinoma			1 (2%)
Neoplastic nodule		1 (2%)	1 (2%)
Osteosarcoma, metastatic, nose	1 (2%)		
Sarcoma, metastatic			1 (2%)
Mesentery	(2)	(10)	(6)
Pancreas	(50)	(50)	(50)
Adenoma	1 (2%)		
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Stomach, forestomach	(49)	(50)	(50)
Papilloma squamous		2 (4%)	6 (12%)
Papilloma squamous, multiple		1 (2%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)
Tongue		(1)	
Papilloma squamous		1 (100%)	
Cardiovascular System			
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	2 (4%)		
Carcinoma	1 (2%)		1 (2%)
Extra adrenal tissue, adenoma		1 (2%)	

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(48)	(50)	(49)
Pheochromocytoma malignant	2 (4%)		1 (2%)
Pheochromocytoma complex			1 (2%)
Pheochromocytoma benign	16 (33%)	11 (22%)	20 (41%)
Bilateral, pheochromocytoma malignant	1 (2%)		
Bilateral, pheochromocytoma benign	5 (10%)	7 (14%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	3 (6%)		
Parathyroid gland	(49)	(44)	(49)
Adenoma		1 (2%)	
Pituitary gland	(50)	(49)	(50)
Pars distalis, adenoma	14 (28%)	4 (8%)	4 (8%)
Pars distalis, carcinoma	1 (2%)		
Pars nervosa, adenoma			1 (2%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	3 (6%)	1 (2%)
C-cell, carcinoma	2 (4%)		
Follicular cell, adenoma	1 (2%)	4 (8%)	
Follicular cell, carcinoma	1 (2%)	2 (4%)	6 (12%)
General Body System			
Tissue NOS	(1)	(1)	
Sarcoma	1 (100%)		
Genital System			
Epididymis	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Preputial gland	(49)	(46)	(48)
Adenoma	3 (6%)	2 (4%)	2 (4%)
Basal cell adenoma	1 (2%)		
Carcinoma			1 (2%)
Papilloma squamous		1 (2%)	
Prostate	(49)	(50)	(50)
Seminal vesicle	(3)		(1)
Testes	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Bilateral, interstitial cell, adenoma	39 (78%)	28 (57%)	24 (48%)
Interstitial cell, adenoma	6 (12%)	9 (18%)	15 (30%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Lymph node	(49)	(48)	(49)
Mandibular, osteosarcoma, metastatic, nose	1 (2%)		
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Mediastinal, hemangiosarcoma		1 (2%)	
Lymph node, mesenteric	(42)	(42)	(44)
Fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Spleen	(50)	(50)	(50)
Sarcoma, metastatic			1 (2%)
Capsule, fibrous histiocytoma, metastatic, uncertain primary site	1 (2%)		
Thymus	(46)	(46)	(45)
Integumentary System			
Mammary gland	(47)	(50)	(45)
Fibroadenoma	2 (4%)		1 (2%)
Skin	(50)	(50)	(50)
Keratoacanthoma	5 (10%)	1 (2%)	
Trichoepithelioma	1 (2%)		1 (2%)
Face, papilloma			1 (2%)
Subcutaneous tissue, fibroma	3 (6%)	1 (2%)	3 (6%)
Tail, neurofibroma			1 (2%)
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Astrocytoma NOS			2 (4%)
Glioma benign	1 (2%)		
Oligodendroglioma benign		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
Carcinoma, metastatic, adrenal gland			1 (2%)
Sarcoma, metastatic			1 (2%)
Alveolar epithelium, carcinoma	1 (2%)		
Nose	(50)	(47)	(50)
Osteosarcoma	1 (2%)		
Mucosa, polyp		1 (2%)	
Trachea	(50)	(50)	(50)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Special Senses System			
Zymbal's gland			(1)
Carcinoma			1 (100%)
Urinary System			
Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
Liposarcoma			1 (2%)
Sarcoma			1 (2%)
Renal tubule, adenoma		2 (4%)	
Urinary bladder	(50)	(50)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia mononuclear	28 (56%)	12 (24%)	14 (28%)
Mesothelioma benign			1 (2%)
Mesothelioma malignant	1 (2%)	1 (2%)	
Mesothelioma NOS		1 (2%)	
Neoplasm Summary			
Total animals with primary neoplasms[c]	49	42	45
Total primary neoplasms	151	101	121
Total animals with benign neoplasms	48	41	44
Total benign neoplasms	109	84	91
Total animals with malignant neoplasms	34	16	23
Total malignant neoplasms	42	16	28
Total animals with metastatic neoplasms	2		2
Total metastatic neoplasms	8		4
Total animals with malignant neoplasms uncertain primary site	1		
Total animals with neoplasms uncertain-benign or malignant		1	2
Total uncertain neoplasms		1	2

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

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

Number of Days on Study	2 7 9	4 8 0	5 0 6	5 4 6	5 5 1	5 6 5	5 7 7	5 8 6	6 0 1	6 0 9	6 3 2	6 3 8	6 5 6	6 5 7	6 7 2	6 8 3	6 9 2	7 0 3	7 0 6	7 0 7	7 1 0	7 1 5	7 1 5	7 1 5	7 2 9
Carcass ID Number	1 0 1	1 1 5	0 8 2	1 2 4	0 7 4	0 4 3	0 4 2	0 9 3	0 7 5	0 1 2	0 8 3	0 2 1	0 3 3	0 9 2	0 3 5	0 5 1	0 6 2	0 0 5	0 5 3	0 1 4	0 6 4	0 2 5	0 4 5	0 2 2	0 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Carcinoma						X										X									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																	X								
Osteosarcoma, metastatic, nose				X																					
Mesentery			+																		+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Fibrous histiocytoma, metastatic, uncertain primary site																								X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign								X		X	X	X	X						X	X				X	
Bilateral, pheochromocytoma malignant																									
Bilateral, pheochromocytoma benign																X	X				X	X	X		

+: 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 Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	7 2 9	7 2 9	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 5 5	0 8 5	0 2 2	0 3 2	0 8 1	0 8 4	1 0 3	1 0 4	1 1 1	1 1 2	0 2 3	0 3 4	0 6 1	0 7 3	0 9 1	0 9 4	0 9 5	1 2 5	0 2 4	0 5 4	0 6 5	0 7 1	0 7 2	1 1 4	1 2 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Osteosarcoma, metastatic, nose																										1
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										16
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												2
Carcinoma															X											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	48
Pheochromocytoma malignant										X													X				2
Pheochromocytoma benign			X			X	X				X				X					X	X				X	16
Bilateral, pheochromocytoma malignant		X																								1
Bilateral, pheochromocytoma benign																										5

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

Number of Days on Study	2 4 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 8 0 4 5 6 7 8 0 0 3 3 5 5 7 8 9 0 0 0 1 1 1 1 2 9 0 6 6 1 5 7 6 1 9 2 8 6 7 2 3 2 3 6 7 0 5 5 5 9
Carcass ID Number	1 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 1 0 0 1 8 2 7 4 4 9 7 1 8 2 3 9 3 5 6 0 5 1 6 2 4 2 3 1 5 2 4 4 3 2 3 5 2 3 1 3 2 5 1 2 5 3 4 4 5 5 2 1
Endocrine System (continued)	
Islets, pancreatic	+ +
Adenoma	
Parathyroid gland	+ M +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X
Pars distalis, carcinoma	X
Thyroid gland	+ +
C-cell, adenoma	X X
C-cell, carcinoma	
Follicular cell, adenoma	
Follicular cell, carcinoma	
General Body System	
Tissue NOS	
Sarcoma	
Genital System	
Epididymis	+ +
Fibrous histiocytoma, metastatic, uncertain primary site	X
Preputial gland	+ + + + + M + + + + + + + + + + + + + + + + + + +
Adenoma	X
Basal cell adenoma	X
Prostate	+ +
Seminal vesicle	+
Testes	+ +
Fibrous histiocytoma, metastatic, uncertain primary site	X
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X
Interstitial cell, adenoma	X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Mandibular, osteosarcoma, metastatic, nose	X
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site	X
Lymph node, mesenteric	+ +
Fibrous histiocytoma, metastatic, uncertain primary site	X

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

Number of Days on Study	7 2 9	7 2 9	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 0 5 5	0 0 8 5	0 0 2 2	0 0 3 2	0 0 8 1	0 0 8 4	1 0 0 3	1 0 4 4	1 1 1 1	1 1 1 2	0 2 2 3	0 3 3 4	0 6 1 1	0 7 3 3	0 9 1 1	0 9 4 4	0 9 5 5	1 2 5 5	0 2 4 4	0 5 6 4	0 6 7 5	0 7 1 1	0 7 2 2	1 1 4 4	1 2 3 3	**Total Tissues/ Tumors**
Endocrine System (continued)																											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X		X			X																3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X			X	X	X				X		X	X												14
Pars distalis, carcinoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma							X											X								X	5
C-cell, carcinoma																						X	X				2
Follicular cell, adenoma																			X								1
Follicular cell, carcinoma								X																			1
General Body System																											
Tissue NOS																			+								1
Sarcoma																			X								1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													X	3
Basal cell adenoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+		49
Seminal vesicle		+																+									3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																											1
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	39
Interstitial cell, adenoma			X									X															6
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Mandibular, osteosarcoma, metastatic, nose																											1
Mediastinal, fibrous histiocytoma, metastatic, uncertain primary site																											1
Lymph node, mesenteric	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	42
Fibrous histiocytoma, metastatic, uncertain primary site																											1

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

Number of Days on Study	2 4 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 8 0 4 5 6 7 8 0 0 3 3 5 5 7 8 9 0 0 0 1 1 1 1 2 9 0 6 6 1 5 7 6 1 9 2 8 6 7 2 3 2 3 6 7 0 5 5 5 9
Carcass ID Number	1 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 1 0 0 1 8 2 7 4 4 9 7 1 8 2 3 9 3 5 6 0 5 1 6 2 4 2 3 1 5 2 4 4 3 2 3 5 2 3 1 3 2 5 1 2 5 3 4 4 5 5 2 1
Hematopoietic System (continued)	
Spleen	+ +
Capsule, fibrous histiocytoma, metastatic, uncertain primary site	X
Thymus	+ +
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + + I + + + + + + + + + +
Fibroadenoma	X
Skin	+ +
Keratoacanthoma	X
Trichoepithelioma	
Subcutaneous tissue, fibroma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Glioma benign	X
Respiratory System	
Lung	+ +
Alveolar epithelium, carcinoma	X
Nose	+ +
Osteosarcoma	X
Trachea	+ +
Special Senses System	
Eye	+
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X X X X X X X X X X X X X X X X
Mesothelioma malignant	X

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

Number of Days on Study	7 2 9	7 2 9	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 5 5	0 8 5	0 2 2	0 3 2	0 8 1	0 8 4	1 0 3	1 0 4	1 1 1	1 1 2	0 2 3	0 3 4	0 6 1	0 7 3	0 9 1	0 9 4	0 9 5	1 2 5	0 2 4	0 5 4	0 6 5	0 7 1	0 7 2	1 1 4	1 2 3	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrous histiocytoma, metastatic, uncertain primary site																										1
Thymus	I	+	+	+	I	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	I	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Fibroadenoma																									X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma		X										X		X								X				5
Trichoepithelioma											X															1
Subcutaneous tissue, fibroma	X			X																		X				3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar epithelium, carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+		+											+												4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X	X	X			X	X	X	X		X	X					X			X			28
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg

Number of Days on Study	0 9 2	1 4 9	1 5 6	1 7 5	2 7 7	2 9 1	3 3 3	3 7 5	3 8 5	3 9 8	5 1 9	5 2 3	5 2 3	5 4 4	5 8 6	6 0 0	6 0 8	6 1 4	6 2 0	6 2 1	6 2 7	6 3 6	6 5 1	6 6 4	6 6 6
Carcass ID Number	2 8 1	3 4 1	3 1 1	2 5 1	2 6 1	2 6 2	2 7 1	3 1 5	3 0 3	2 7 4	2 7 3	2 5 4	3 5 1	2 5 2	3 5 2	2 8 5	2 8 3	3 2 4	3 6 3	3 6 4	2 7 5	2 9 5	3 0 2	2 7 2	2 6 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mesentery																					+				+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								X	
Papilloma squamous, multiple																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Extra adrenal tissue, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X				X						X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 6 6 6 6 7 8 8 8 9 9 9 9 9 0 1 2 2 2 3 3 3 3 3 3 3 6 6 7 9 1 0 0 5 0 1 3 5 7 3 1 9 9 9 2 2 2 3 3 4 4	
Carcass ID Number	2 3 3 2 3 2 2 3 3 3 3 2 3 3 3 2 3 3 2 3 3 3 3 3 3 8 0 2 6 4 5 8 1 0 4 1 9 6 4 4 6 3 3 9 1 6 3 5 3 5 4 5 5 3 3 3 2 3 1 2 4 3 1 4 5 4 2 3 1 2 2 5 5 4 4	**Total Tissues/ Tumors**
Alimentary System		
Esophagus	+ +	50
Intestine large	+ +	50
Intestine large, cecum	+ +	50
Intestine large, colon	+ +	50
Intestine large, rectum	+ + + + + + + + + + + + + + + I + + M + + + + + +	46
Intestine small	+ +	50
Intestine small, duodenum	+ +	49
Intestine small, ileum	+ +	50
Intestine small, jejunum	+ +	50
Liver	+ +	50
Neoplastic nodule	X	1
Mesentery	+ + + + + + + + + +	10
Pancreas	+ +	50
Salivary glands	+ +	50
Stomach, forestomach	+ +	50
Papilloma squamous	X	2
Papilloma squamous, multiple	X	1
Stomach, glandular	+ +	50
Tongue	+	1
Papilloma squamous	X	1
Cardiovascular System		
Blood vessel	+ +	41
Heart	+ +	50
Endocrine System		
Adrenal gland	+ +	50
Adrenal gland, cortex	+ +	50
Extra adrenal tissue, adenoma	X	1
Adrenal gland, medulla	+ +	50
Pheochromocytoma benign	X X X X X X X	11
Bilateral, pheochromocytoma benign	X X X X X X	7
Islets, pancreatic	+ +	50
Parathyroid gland	M + + + M +	44
Adenoma	X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	0	1	1	1	2	2	3	3	3	3	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	9	4	5	7	7	9	3	7	8	9	1	2	2	4	8	0	0	1	2	2	2	3	5	6	6
	2	9	6	5	7	1	3	5	5	8	9	3	3	4	6	0	8	4	0	1	7	6	1	4	6
Carcass ID Number	2	3	3	2	2	2	2	3	3	2	2	2	3	2	3	2	2	3	3	3	2	2	3	2	2
	8	4	1	5	6	6	7	1	0	7	7	5	5	5	5	8	8	2	6	6	7	9	0	7	6
	1	1	1	1	1	2	1	5	3	4	3	4	1	2	2	5	3	4	3	4	5	5	2	2	5
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
Follicular cell, adenoma																					X	X		X	
Follicular cell, carcinoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+
Adenoma																									
Papilloma squamous														X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma												X		X	X	X		X	X	X		X	X	X	
Interstitial cell, adenoma													X				X				X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, hemangiosarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Skeletal muscle																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 6 6 6 6 7 8 8 8 9 9 9 9 9 0 1 2 2 2 3 3 3 3 3 3 3 6 6 7 9 1 0 0 5 0 1 3 5 7 3 1 9 9 9 2 2 2 3 3 4 4	
Carcass ID Number	2 3 3 2 3 2 2 3 3 3 3 2 3 3 3 2 3 3 2 3 3 3 3 3 3 8 0 2 6 4 5 8 1 0 4 1 9 6 4 4 6 3 3 9 1 6 3 5 3 5 4 5 5 3 3 3 2 3 1 2 4 3 1 4 5 4 2 3 1 2 2 5 5 4 4	**Total Tissues/ Tumors**
Endocrine System (continued)		
Pituitary gland	+ + + + + + + + + + + + + + + + + + + M + + + + +	49
Pars distalis, adenoma	X X X X	4
Thyroid gland	+ +	50
C-cell, adenoma	X X	3
Follicular cell, adenoma	X	4
Follicular cell, carcinoma	X X	2
General Body System		
Tissue NOS	+	1
Genital System		
Epididymis	+ + + + M +	49
Preputial gland	+ + + + M + + + + + + + + + + + + + + + + + M + +	46
Adenoma	X X	2
Papilloma squamous		1
Prostate	+ +	50
Testes	+ + + + M +	49
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X X X X X X X X X	28
Interstitial cell, adenoma	X X X X X X X	9
Hematopoietic System		
Bone marrow	+ +	49
Lymph node	+ +	48
Mediastinal, hemangiosarcoma	X	1
Lymph node, mesenteric	+ +	42
Spleen	+ +	50
Thymus	+ + + + I + + + + + + + + + + I + + + I + + + M +	46
Integumentary System		
Mammary gland	+ +	50
Skin	+ +	50
Keratoacanthoma	X	1
Subcutaneous tissue, fibroma		1
Musculoskeletal System		
Bone	+ +	49
Skeletal muscle	+	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	0	1	1	1	2	2	3	3	3	3	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6
	9	4	5	7	7	9	3	7	8	9	1	2	2	4	8	0	0	1	2	2	2	3	5	6	6
	2	9	6	5	7	1	3	5	5	8	9	3	3	4	6	0	8	4	0	1	7	6	1	4	6
Carcass ID Number	2	3	3	2	2	2	2	3	3	2	2	2	3	2	3	2	2	3	3	3	2	2	3	2	2
	8	4	1	5	6	6	7	1	0	7	7	5	5	5	5	8	8	2	6	6	7	9	0	7	6
	1	1	1	1	1	2	1	5	3	4	3	4	1	2	2	5	3	4	3	4	5	5	2	2	5
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign								X																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	I	+
Mucosa, polyp																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																			+						
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																								X	
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X					X			X		X	X			
Mesothelioma malignant																									
Mesothelioma NOS																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	6 6 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 6 6 6 7 7 8 8 8 9 9 9 9 9 0 1 2 2 2 3 3 3 3 3 3 3 6 6 7 9 1 0 0 5 0 1 3 5 7 3 1 9 9 9 2 2 2 3 3 4 4	
Carcass ID Number	2 3 3 2 3 2 2 3 3 3 3 2 3 3 3 2 3 3 2 3 3 3 3 3 3 8 0 2 6 4 5 8 1 0 4 1 9 6 4 4 6 3 3 9 1 6 3 5 3 5 4 5 5 3 3 3 2 3 1 2 4 3 1 4 5 4 2 3 1 2 2 5 5 4 4	**Total Tissues/ Tumors**
Nervous System		
Brain	+ +	50
Oligodendroglioma benign		1
Respiratory System		
Lung	+ +	50
Alveolar/bronchiolar adenoma	X	1
Nose	+ +	47
Mucosa, polyp	X	1
Trachea	+ +	50
Special Senses System		
Ear		1
Eye	+	1
Urinary System		
Kidney	+ +	50
Lipoma		1
Renal tubule, adenoma	X X	2
Urinary bladder	+ +	50
Systemic Lesions		
Multiple organs	+ +	50
Leukemia mononuclear	X X X X X X X	12
Mesothelioma malignant	X	1
Mesothelioma NOS	X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg

Number of Days on Study	1 7 3	3 6 1	3 6 3	4 1 1	4 7 0	4 9 0	5 0 7	5 2 6	5 5 4	5 6 5	5 6 9	5 6 3	5 7 3	5 7 3	5 8 6	5 9 5	5 9 5	5 9 5	6 0 6	6 1 0	6 1 9	6 2 1	6 2 3	6 3 3	6 3 3
Carcass ID Number	5 5 1	5 9 2	4 9 4	5 0 4	5 2 4	5 8 3	4 9 2	5 2 5	5 0 2	5 0 1	5 6 5	5 0 5	5 1 4	5 7 4	5 1 3	5 1 5	5 9 1	5 5 2	6 0 2	6 0 3	5 2 2	5 1 1	5 3 5	5 4 2	5 5 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Neoplastic nodule																									
Sarcoma, metastatic																							X		
Mesentery			+					+							+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous						X															X				
Papilloma squamous, multiple									X		X	X			X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									
Pheochromocytoma benign								X	X		X	X	X					X	X		X			X	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	6 3 8	6 3 8	6 4 4	6 4 4	6 5 2	6 5 8	6 6 4	6 6 7	6 6 7	6 6 7	6 6 9	6 7 6	6 7 6	6 8 7	6 9 2	7 0 3	7 1 0	7 1 5	7 1 9	7 1 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 3	
Carcass ID Number	5 7 2	6 0 4	4 9 3	5 4 4	5 5 4	5 0 3	4 9 5	4 9 1	5 8 1	5 9 4	5 7 1	5 1 2	6 0 1	5 7 3	6 0 5	5 3 4	5 9 3	5 4 1	5 2 1	5 8 5	5 3 2	5 4 5	5 6 3	5 7 5	5 3 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																							X			1
Neoplastic nodule																			X							1
Sarcoma, metastatic																										1
Mesentery						+													+					+		6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																X			X		X			X		6
Papilloma squamous, multiple	X																X									6
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									42
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant				X																						1
Pheochromocytoma complex																				X						1
Pheochromocytoma benign			X	X				X	X		X			X		X				X	X	X			X	20
Bilateral, pheochromocytoma benign												X						X	X							3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	1 3 3 4 4 4 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 7 6 6 1 7 9 0 2 5 6 6 7 7 7 8 9 9 9 0 1 1 2 2 3 3 3 1 3 1 0 0 7 6 4 5 9 3 3 3 6 5 5 9 6 0 9 1 3 3 3
Carcass ID Number	5 5 4 5 5 5 4 5 5 5 5 5 5 5 5 5 5 5 6 6 5 5 5 5 5 5 9 9 0 2 8 9 2 0 0 6 0 1 7 1 1 9 5 0 0 2 1 3 4 5 1 2 4 4 4 3 2 5 2 1 5 5 4 4 3 5 1 2 2 3 2 1 5 2 5
Endocrine System (continued)	
Parathyroid gland	+ + M +
Pituitary gland	+ +
Pars distalis, adenoma	X X
Pars nervosa, adenoma	
Thyroid gland	+ +
C-cell, adenoma	
Follicular cell, carcinoma	X X X X
General Body System	
None	
Genital System	
Epididymis	+ +
Preputial gland	+ M + +
Adenoma	X
Carcinoma	
Prostate	+ +
Seminal vesicle	
Testes	+ +
Bilateral, interstitial cell, adenoma	X X X X X X X X X X
Interstitial cell, adenoma	X X X X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mesenteric	+ + M +
Spleen	+ +
Sarcoma, metastatic	X
Thymus	+ + + I + + + + + + I + + + + I + + + I + + + + +
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + + + + + + + M + + + + +
Fibroadenoma	X
Skin	+ +
Trichoepithelioma	
Face, papilloma	X
Subcutaneous tissue, fibroma	
Tail, neurofibroma	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	6 3 8	6 3 8	6 4 4	6 4 4	6 5 2	6 5 8	6 6 4	6 6 7	6 6 7	6 6 7	6 6 9	6 7 6	6 7 6	6 8 7	6 9 2	7 0 3	7 1 0	7 1 5	7 1 9	7 1 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 3	
Carcass ID Number	5 7 2	6 0 4	4 9 3	5 4 4	5 5 4	5 0 3	4 9 5	4 9 1	5 8 1	5 9 4	5 7 1	5 1 2	6 0 1	5 7 3	6 0 5	5 3 4	5 9 3	5 4 1	5 2 1	5 8 5	5 3 2	5 4 5	5 6 3	5 7 5	5 3 1	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma									X													X				4
Pars nervosa, adenoma							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																								X		1
Follicular cell, carcinoma																X				X						6
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																									2
Carcinoma																					X					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle																		+								1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X				X		X	X	X	X		X	X		X	X	X	X	X			X			24
Interstitial cell, adenoma				X	X		X					X			X							X	X		X	X	15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+	+	+		+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	I	I	+	+	+	+	+	45
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trichoepithelioma			X																							1
Face, papilloma																										1
Subcutaneous tissue, fibroma															X						X			X		3
Tail, neurofibroma														X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	1	3	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	
	7	6	6	1	7	9	0	2	5	6	6	7	7	7	8	9	9	9	0	1	1	2	2	3	3
	3	1	3	1	0	0	7	6	4	5	9	3	3	3	6	5	5	9	6	0	9	1	3	3	3
Carcass ID Number	5	5	4	5	5	5	4	5	5	5	5	5	5	5	5	5	5	5	6	6	5	5	5	5	5
	5	9	9	0	2	8	9	2	0	0	6	0	1	7	1	1	9	5	0	0	2	1	3	4	5
	1	2	4	4	4	3	2	5	2	1	5	5	4	4	3	5	1	2	2	3	2	1	5	2	5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																									X
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, adrenal gland															X										
Sarcoma, metastatic																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																									
Sarcoma																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	6 3 8	6 3 8	6 4 4	6 4 4	6 5 2	6 5 8	6 6 4	6 6 7	6 6 7	6 6 7	6 6 9	6 7 6	6 7 6	6 8 7	6 9 2	7 0 3	7 1 0	7 1 5	7 1 9	7 1 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 3	
Carcass ID Number	5 7 2	6 0 4	4 0 3	5 4 4	5 5 4	5 0 3	4 9 5	4 9 1	5 8 1	5 9 4	5 7 1	5 1 2	6 0 1	5 7 3	6 0 5	5 3 4	5 9 3	5 4 1	5 2 1	5 8 5	5 3 2	5 4 5	5 6 3	5 7 5	5 3 1	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle						+																				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS																		X								2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, adrenal gland																										1
Sarcoma, metastatic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland												+														1
Carcinoma												X														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma																								X		1
Sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X										X	X		X			X					14
Mesothelioma benign																										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	21/48 (44%)	18/50 (36%)	23/49 (47%)
Adjusted rates[b]	55.0%	88.2%	88.8%
Terminal rates[c]	8/24 (33%)	8/10 (80%)	3/5 (60%)
First incidence (days)	586	544	526
Life table tests[d]	P<0.001	P=0.037	P<0.001
Logistic regression tests[d]	P=0.074	P=0.401	P=0.156
Cochran-Armitage test[d]	P=0.412		
Fisher exact test[d]		P=0.282N	P=0.456
Adrenal Medulla: Malignant Pheochromocytoma			
Overall rates	3/48 (6%)	0/50 (0%)	1/49 (2%)
Adjusted rates	12.5%	0.0%	4.3%
Terminal rates	3/24 (13%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	–[e]	644
Life table tests	P=0.536N	P=0.309N	P=0.690
Logistic regression tests	P=0.363N	P=0.309N	P=0.568N
Cochran-Armitage test	P=0.170N		
Fisher exact test		P=0.114N	P=0.301N
Adrenal Medulla: Pheochromocytoma (Benign, Complex, or Malignant)			
Overall rates	24/48 (50%)	18/50 (36%)	23/49 (47%)
Adjusted rates	63.4%	88.2%	88.8%
Terminal rates	11/24 (46%)	8/10 (80%)	3/5 (60%)
First incidence (days)	586	544	526
Life table tests	P<0.001	P=0.073	P<0.001
Logistic regression tests	P=0.178	P=0.570N	P=0.293
Cochran-Armitage test	P=0.424N		
Fisher exact test		P=0.116N	P=0.461N
Pancreatic Islets: Adenoma			
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rates	11.5%	0.0%	0.0%
Terminal rates	3/26 (12%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	–	–
Life table tests	P=0.208N	P=0.329N	P=0.510N
Logistic regression tests	P=0.208N	P=0.329N	P=0.510N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.121N	P=0.121N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	14/50 (28%)	4/49 (8%)	4/50 (8%)
Adjusted rates	42.8%	28.2%	29.1%
Terminal rates	9/26 (35%)	2/9 (22%)	1/5 (20%)
First incidence (days)	506	666	595
Life table tests	P=0.369N	P=0.293N	P=0.502N
Logistic regression tests	P=0.026N	P=0.053N	P=0.038N
Cochran-Armitage test	P=0.004N		
Fisher exact test		P=0.010N	P=0.009N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	15/50 (30%)	4/49 (8%)	4/50 (8%)
Adjusted rates	43.9%	28.2%	29.1%
Terminal rates	9/26 (35%)	2/9 (22%)	1/5 (20%)
First incidence (days)	480	666	595
Life table tests	P=0.271N	P=0.220N	P=0.392N
Logistic regression tests	P=0.009N	P=0.024N	P=0.014N
Cochran-Armitage test	P=0.002N		
Fisher exact test		P=0.005N	P=0.005N
Preputial Gland: Adenoma			
Overall rates	3/49 (6%)	2/46 (4%)	2/48 (4%)
Adjusted rates	9.8%	17.0%	6.9%
Terminal rates	2/26 (8%)	1/9 (11%)	0/5 (0%)
First incidence (days)	586	693	599
Life table tests	P=0.351	P=0.516	P=0.543
Logistic regression tests	P=0.533N	P=0.685	P=0.545N
Cochran-Armitage test	P=0.416N		
Fisher exact test		P=0.530N	P=0.510N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	3/49 (6%)	2/46 (4%)	3/48 (6%)
Adjusted rates	9.8%	17.0%	25.5%
Terminal rates	2/26 (8%)	1/9 (11%)	1/5 (20%)
First incidence (days)	586	693	599
Life table tests	P=0.139	P=0.516	P=0.244
Logistic regression tests	P=0.420	P=0.685	P=0.579
Cochran-Armitage test	P=0.578		
Fisher exact test		P=0.530N	P=0.651
Skin: Keratoacanthoma			
Overall rates	5/50 (10%)	1/50 (2%)	0/50 (0%)
Adjusted rates	17.7%	6.7%	0.0%
Terminal rates	4/26 (15%)	0/10 (0%)	0/5 (0%)
First incidence (days)	672	693	–
Life table tests	P=0.159N	P=0.398N	P=0.304N
Logistic regression tests	P=0.067N	P=0.265N	P=0.162N
Cochran-Armitage test	P=0.011N		
Fisher exact test		P=0.102N	P=0.028N
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rates	11.5%	2.5%	45.5%
Terminal rates	3/26 (12%)	0/10 (0%)	2/5 (40%)
First incidence (days)	729 (T)	519	692
Life table tests	P=0.093	P=0.591N	P=0.049
Logistic regression tests	P=0.362	P=0.383N	P=0.125
Cochran-Armitage test	P=0.594		
Fisher exact test		P=0.309N	P=0.661N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rates	0/50 (0%)	3/50 (6%)	12/50 (24%)
Adjusted rates	0.0%	17.7%	66.3%
Terminal rates	0/26 (0%)	1/10 (10%)	2/5 (40%)
First incidence (days)	–	664	490
Life table tests	P<0.001	P=0.041	P<0.001
Logistic regression tests	P<0.001	P=0.066	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.121	P<0.001
Testes: Adenoma			
Overall rates	45/50 (90%)	37/49 (76%)	39/50 (78%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	10/10 (100%)	5/5 (100%)
First incidence (days)	546	523	470
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P=0.482N	P=0.380	P=0.608N
Cochran-Armitage test	P=0.080N		
Fisher exact test		P=0.049N	P=0.086N
Thyroid Gland (C-cell): Adenoma			
Overall rates	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rates	17.7%	18.9%	20.0%
Terminal rates	4/26 (15%)	1/10 (10%)	1/5 (20%)
First incidence (days)	657	608	729 (T)
Life table tests	P=0.551N	P=0.520	P=0.648N
Logistic regression tests	P=0.258N	P=0.583N	P=0.428N
Cochran-Armitage test	P=0.070N		
Fisher exact test		P=0.357N	P=0.102N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	7/50 (14%)	3/50 (6%)	1/50 (2%)
Adjusted rates	25.2%	18.9%	20.0%
Terminal rates	6/26 (23%)	1/10 (10%)	1/5 (20%)
First incidence (days)	657	608	729 (T)
Life table tests	P=0.379N	P=0.610N	P=0.508N
Logistic regression tests	P=0.135N	P=0.388N	P=0.295N
Cochran-Armitage test	P=0.017N		
Fisher exact test		P=0.159N	P=0.030N
Thyroid Gland (Follicular Cell): Adenoma			
Overall rates	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rates	3.8%	18.3%	0.0%
Terminal rates	1/26 (4%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	627	–
Life table tests	P=0.513	P=0.059	P=0.821N
Logistic regression tests	P=0.490N	P=0.116	P=0.821N
Cochran-Armitage test	P=0.390N		
Fisher exact test		P=0.181	P=0.500N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Thyroid Gland (Follicular Cell): Carcinoma			
Overall rates	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rates	3.8%	11.6%	31.9%
Terminal rates	1/26 (4%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	671	569
Life table tests	P=0.002	P=0.244	P=0.005
Logistic regression tests	P=0.017	P=0.368	P=0.044
Cochran-Armitage test	P=0.029		
Fisher exact test		P=0.500	P=0.056
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	2/50 (4%)	6/50 (12%)	6/50 (12%)
Adjusted rates	7.7%	27.7%	31.9%
Terminal rates	2/26 (8%)	0/10 (0%)	0/5 (0%)
First incidence (days)	729 (T)	627	569
Life table tests	P=0.006	P=0.020	P=0.010
Logistic regression tests	P=0.062	P=0.061	P=0.091
Cochran-Armitage test	P=0.114		
Fisher exact test		P=0.134	P=0.134
All Organs: Mononuclear Cell Leukemia			
Overall rates	28/50 (56%)	12/50 (24%)	14/50 (28%)
Adjusted rates	67.6%	67.3%	58.8%
Terminal rates	13/26 (50%)	6/10 (60%)	1/5 (20%)
First incidence (days)	546	398	361
Life table tests	P=0.303	P=0.395N	P=0.304
Logistic regression tests	P=0.014N	P=0.011N	P=0.016N
Cochran-Armitage test	P=0.002N		
Fisher exact test		P=0.001N	P=0.004N
All Organs: Benign Neoplasms			
Overall rates	48/50 (96%)	41/50 (82%)	44/50 (88%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	10/10 (100%)	5/5 (100%)
First incidence (days)	506	375	470
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P=0.415N	P=0.425	P=0.671N
Cochran-Armitage test	P=0.135N		
Fisher exact test		P=0.026N	P=0.134N
All Organs: Malignant Neoplasms			
Overall rates	34/50 (68%)	16/50 (32%)	23/50 (46%)
Adjusted rates	76.8%	79.8%	85.9%
Terminal rates	16/26 (62%)	7/10 (70%)	3/5 (60%)
First incidence (days)	480	398	361
Life table tests	P=0.027	P=0.499N	P=0.033
Logistic regression tests	P=0.085N	P=0.006N	P=0.068N
Cochran-Armitage test	P=0.018N		
Fisher exact test		P<0.001N	P=0.021N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
All Organs: Benign or Malignant Neoplasms			
Overall rates	49/50 (98%)	42/50 (84%)	45/50 (90%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	26/26 (100%)	10/10 (100%)	5/5 (100%)
First incidence (days)	480	375	361
Life table tests	P<0.001	P=0.002	P<0.001
Logistic regression tests	P=0.183N	P=0.669N	P=0.382N
Cochran-Armitage test	P=0.114N		
Fisher exact test		P=0.015N	P=0.102N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, 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 neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column 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 neoplasms 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 neoplasms in animal group

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Male F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/50	0/50	0/50
Overall Historical Incidence			
Total	2/263 (0.8%)	0/263 (0.0%)	2/263 (0.8%)
Standard deviation	1.3%		1.3%
Range	0%-3%		0%-3%

[a] Data as of 17 September 1990

TABLE A4b
Historical Incidence of Forestomach Neoplasms in Male F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/264 (0.4%)	0/264 (0.0%)	1/264 (0.4%)
Standard deviation	0.9%		0.9%
Range	0%-2%		0%-2%

[a] Data as of 17 September 1990

TABLE A4c
Historical Incidence of Thyroid Follicular Cell Neoplasms in Male F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/49	1/49	1/49
Overall Historical Incidence			
Total	1/259 (0.4%)	1/259 (0.4%)	4/259[b] (1.5%)
Standard deviation	0.9%	0.9%	2.2%
Range	0%-2%	0%-2%	0%-5%

[a] Data as of 17 September 1990
[b] Includes data for two adenocarcinomas

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	2.5 mg/kg	5 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	20	19	32
Natural deaths	4	21	13
Survivors			
Terminal sacrifice	26	10	5
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, cecum	(50)	(50)	(50)
Autolysis		3 (6%)	2 (4%)
Congestion			2 (4%)
Edema	1 (2%)	1 (2%)	
Hemorrhage		3 (6%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
Inflammation, acute		6 (12%)	7 (14%)
Inflammation, chronic	1 (2%)	2 (4%)	3 (6%)
Parasite metazoan			1 (2%)
Ulcer		8 (16%)	4 (8%)
Intestine large, colon	(50)	(50)	(50)
Autolysis		2 (4%)	1 (2%)
Hyperplasia, lymphoid			2 (4%)
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)		3 (6%)
Mineralization		2 (4%)	
Parasite metazoan	1 (2%)	8 (16%)	5 (10%)
Intestine large, rectum	(50)	(46)	(50)
Autolysis		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, acute, chronic			1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)	2 (4%)
Mineralization		1 (2%)	
Parasite metazoan		4 (9%)	
Ulcer		1 (2%)	1 (2%)
Intestine small, duodenum	(50)	(49)	(50)
Autolysis		4 (8%)	2 (4%)
Necrosis	1 (2%)		
Intestine small, ileum	(49)	(50)	(49)
Autolysis		5 (10%)	3 (6%)
Hyperplasia, lymphoid	4 (8%)		
Inflammation, chronic		1 (2%)	
Ulcer		1	(2%)
Intestine small, jejunum	(49)	(50)	(50)
Autolysis		9 (18%)	4 (8%)
Metaplasia, osseous	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Alimentary System (continued)			
Liver	(50)	(50)	(50)
Angiectasis		6 (12%)	
Autolysis		1 (2%)	
Basophilic focus			1 (2%)
Basophilic focus, multiple	17 (34%)	7 (14%)	6 (12%)
Clear cell focus	1 (2%)		
Congestion	2 (4%)	3 (6%)	1 (2%)
Cyst	1 (2%)		
Cytoplasmic alteration, focal	7 (14%)	3 (6%)	2 (4%)
Ectasia	2 (4%)	1 (2%)	
Eosinophilic focus	1 (2%)	2 (4%)	2 (4%)
Fibrosis, focal	1 (2%)		
Hematopoietic cell proliferation	1 (2%)		
Hepatodiaphragmatic nodule	8 (16%)	6 (12%)	7 (14%)
Hyperplasia, focal	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, granulomatous, multifocal	1 (2%)		
Necrosis, acute	4 (8%)	6 (12%)	11 (22%)
Thrombus, focal	1 (2%)		
Vacuolization cytoplasmic, focal	3 (6%)	1 (2%)	
Bile duct, hyperplasia	17 (34%)	22 (44%)	15 (30%)
Hepatocyte, degeneration, cystic	5 (10%)	7 (14%)	4 (8%)
Mesentery	(2)	(10)	(6)
Hemorrhage, focal		1 (10%)	
Inflammation, acute, focal			1 (17%)
Inflammation, chronic		1 (10%)	
Fat, necrosis		1 (10%)	1 (17%)
Fat, necrosis, focal	2 (100%)	8 (80%)	3 (50%)
Pancreas	(50)	(50)	(50)
Atrophy, focal	25 (50%)	15 (30%)	18 (36%)
Autolysis		2 (4%)	2 (4%)
Cytoplasmic alteration, focal	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, granulomatous, focal			1 (2%)
Artery, inflammation, chronic		1 (2%)	
Salivary glands	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Duct, hyperplasia	1 (2%)		
Duct, metaplasia, squamous			1 (2%)
Stomach	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)
Autolysis			1 (2%)
Cyst epithelial inclusion			1 (2%)
Edema	2 (4%)		
Hyperplasia	3 (6%)	16 (32%)	35 (70%)
Inflammation, acute	2 (4%)	2 (4%)	4 (8%)
Mineralization		5 (10%)	2 (4%)
Ulcer	1 (2%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Alimentary System (continued)			
Stomach, glandular	(50)	(50)	(50)
Autolysis			1 (2%)
Hyperplasia	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic		2 (4%)	1 (2%)
Mineralization		9 (18%)	5 (10%)
Necrosis	3 (6%)	2 (4%)	5 (10%)
Ulcer		1 (2%)	1 (2%)
Cardiovascular System			
Blood vessel	(16)	(41)	(42)
Mineralization		6 (15%)	2 (5%)
Heart	(50)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic	44 (88%)	48 (96%)	48 (96%)
Mineralization		13 (26%)	14 (28%)
Atrium left, thrombus	1 (2%)	5 (10%)	2 (4%)
Endocardium, fibrosis	1 (2%)		
Epicardium, inflammation, chronic, focal	1 (2%)		
Valve, thrombus	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Congestion	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, focal	10 (20%)	3 (6%)	8 (16%)
Hypertrophy, focal	5 (10%)		1 (2%)
Inflammation, chronic, multifocal			1 (2%)
Mineralization, multifocal			1 (2%)
Vacuolization cytoplasmic	10 (20%)	8 (16%)	10 (20%)
Capsule, ectopic tissue			1 (2%)
Adrenal gland, medulla	(48)	(50)	(49)
Hyperplasia, focal	8 (17%)	8 (16%)	6 (12%)
Thrombus	1 (2%)		
Bilateral, hyperplasia, focal	1 (2%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)
Autolysis		2 (4%)	1 (2%)
Hyperplasia	3 (6%)		2 (4%)
Parathyroid gland	(49)	(44)	(49)
Hyperplasia	2 (4%)	23 (52%)	19 (39%)
Hyperplasia, focal		2 (5%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Pars distalis, angiectasis	2 (4%)	2 (4%)	1 (2%)
Pars distalis, cyst	1 (2%)	4 (8%)	
Pars distalis, cytoplasmic alteration, focal	1 (2%)		
Pars distalis, ectasia	1 (2%)		
Pars distalis, hyperplasia	12 (24%)	9 (18%)	6 (12%)
Pars distalis, hypertrophy	2 (4%)	2 (4%)	
Pars distalis, necrosis, focal	1 (2%)		
Pars nervosa, cyst		1 (2%)	1 (2%)
Pars nervosa, hyperplasia		3 (6%)	
Pars nervosa, inflammation, granulomatous			1 (2%)
Thyroid gland	(50)	(50)	(50)
Hemorrhage		2 (4%)	
Ultimobranchial cyst	1 (2%)	1 (2%)	1 (2%)
C-cell, hyperplasia	6 (12%)	2 (4%)	1 (2%)
Follicle, cyst	1 (2%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia	2 (4%)	3 (6%)	2 (4%)
Follicular cell, hyperplasia, cystic		1 (2%)	
General Body System			
None			
Genital System			
Epididymis	(50)	(49)	(50)
Cytomegaly		1 (2%)	
Duct, epithelium, degeneration	1 (2%)	3 (6%)	2 (4%)
Fat, necrosis, focal	3 (6%)		
Preputial gland	(49)	(46)	(48)
Hyperplasia	2 (4%)		
Inflammation, acute	11 (22%)	12 (26%)	9 (19%)
Inflammation, chronic	9 (18%)	2 (4%)	8 (17%)
Inflammation, chronic active	2 (4%)		
Duct, ectasia	1 (2%)	2 (4%)	
Duct, hyperplasia			1 (2%)
Prostate	(49)	(50)	(50)
Hyperplasia, focal	8 (16%)	1 (2%)	
Inflammation, acute	5 (10%)	4 (8%)	1 (2%)
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)
Inflammation, chronic active	3 (6%)	1 (2%)	
Testes	(50)	(49)	(50)
Atrophy	3 (6%)	3 (6%)	1 (2%)
Bilateral, atrophy			2 (4%)
Bilateral, interstitial cell, hyperplasia	3 (6%)	1 (2%)	1 (2%)
Interstitial cell, hyperplasia	3 (6%)	4 (8%)	8 (16%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Congestion			1 (2%)
Depletion, focal			2 (4%)
Hypoplasia	1 (2%)		
Myelofibrosis			1 (2%)
Myeloid cell, hyperplasia	5 (10%)	5 (10%)	4 (8%)
Lymph node	(49)	(48)	(49)
Granuloma		1 (2%)	
Inflammation		1 (2%)	
Axillary, congestion	1 (2%)		
Axillary, hemorrhage	1 (2%)		
Iliac, hyperplasia			1 (2%)
Inguinal, hyperplasia, lymphoid	1 (2%)		1 (2%)
Mandibular, hemorrhage		1 (2%)	
Mandibular, inflammation, acute, focal		1 (2%)	
Mediastinal, hyperplasia			1 (2%)
Mediastinal, infiltration cellular, plasma cell	1 (2%)		
Renal, hemorrhage			1 (2%)
Renal, hyperplasia			1 (2%)
Renal, pigmentation			1 (2%)
Lymph node, mesenteric	(42)	(42)	(44)
Autolysis		1 (2%)	
Congestion			1 (2%)
Ectasia	1 (2%)		
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia		1 (2%)	
Hyperplasia, lymphoid	2 (5%)	1 (2%)	2 (5%)
Hyperplasia, plasma cell		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		2 (5%)	
Spleen	(50)	(50)	(50)
Atrophy, focal		1 (2%)	1 (2%)
Congestion	4 (8%)	1 (2%)	
Fibrosis	2 (4%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation		2 (4%)	1 (2%)
Hematopoietic cell proliferation granulocytic	2 (4%)	1 (2%)	2 (4%)
Necrosis, focal			1 (2%)
Pigmentation		1 (2%)	
Capsule, fibrosis		1 (2%)	1 (2%)
Thymus	(46)	(46)	(45)
Autolysis			1 (2%)
Congestion	1 (2%)	3 (7%)	
Cyst	3 (7%)		1 (2%)
Ectopic parathyroid gland	1 (2%)		
Hemorrhage		1 (2%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Integumentary System			
Mammary gland	(47)	(50)	(45)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)
Duct, ectasia	5 (11%)	2 (4%)	1 (2%)
Skin	(50)	(50)	(50)
Cyst	2 (4%)		
Hyperkeratosis			1 (2%)
Face, inflammation, acute	2 (4%)		4 (8%)
Tail, hemorrhage			1 (2%)
Tail, subcutaneous tissue, necrosis			1 (2%)
Musculoskeletal System			
Bone	(50)	(49)	(50)
Fibrous osteodystrophy	1 (2%)	27 (55%)	21 (42%)
Osteomalacia			1 (2%)
Skeletal muscle		(1)	(1)
Hemorrhage		1 (100%)	
Inflammation, acute, focal			1 (100%)
Nervous System			
Brain	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Hydrocephalus	4 (8%)		
Inflammation, acute, focal	1 (2%)		
Meninges, congestion		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	8 (16%)	13 (26%)	5 (10%)
Fibrosis, focal		1 (2%)	1 (2%)
Foreign body	1 (2%)		
Hemorrhage	5 (10%)	4 (8%)	5 (10%)
Inflammation, acute, chronic		1 (2%)	
Inflammation, acute, multifocal	1 (2%)	5 (10%)	1 (2%)
Inflammation, chronic	4 (8%)	3 (6%)	3 (6%)
Inflammation, granulomatous	2 (4%)		1 (2%)
Metaplasia, osseous, focal	1 (2%)		
Necrosis, focal	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	5 (10%)
Alveolus, infiltration cellular, histiocyte		3 (6%)	1 (2%)
Artery, media, hypertrophy	1 (2%)		
Perivascular, infiltration cellular, lymphocyte	1 (2%)	2 (4%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Respiratory System (continued)			
Nose	(50)	(47)	(50)
Autolysis	1 (2%)	6 (13%)	6 (12%)
Foreign body	1 (2%)	3 (6%)	2 (4%)
Fungus	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Hyperplasia, squamous		1 (2%)	
Inflammation, chronic active			1 (2%)
Mucosa, cyst	1 (2%)		
Mucosa, inflammation, acute		4 (9%)	2 (4%)
Mucosa, inflammation, chronic	2 (4%)		
Mucosa, inflammation, chronic active	7 (14%)	4 (9%)	16 (32%)
Nasolacrimal duct, cyst		1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)		3 (6%)
Nasolacrimal duct, inflammation, chronic	3 (6%)		1 (2%)
Respiratory epithelium, hyperplasia	5 (10%)	1 (2%)	3 (6%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)	
Trachea	(50)	(50)	(50)
Inflammation, acute			2 (4%)
Special Senses System			
Eye	(4)	(1)	
Hemorrhage	1 (25%)		
Bilateral, lens, cataract		1 (100%)	
Lens, cataract	1 (25%)		
Retina, degeneration	3 (75%)		
Sclera, inflammation, acute	1 (25%)		
Urinary System			
Kidney	(50)	(50)	(50)
Congestion		3 (6%)	1 (2%)
Inflammation, acute, focal	1 (2%)	1 (2%)	
Mineralization			3 (6%)
Nephropathy	50 (100%)	46 (92%)	48 (96%)
Pigmentation	2 (4%)		
Cortex, cyst	3 (6%)	5 (10%)	4 (8%)
Renal tubule, hyperplasia	1 (2%)		3 (6%)
Renal tubule, hyperplasia, cystic		1 (2%)	1 (2%)
Urinary bladder	(50)	(50)	(50)
Concretion	1 (2%)		

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF MERCURIC CHLORIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	2.5 mg/kg	5 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	14	14	9
Natural deaths	1	7	11
Survivors			
Died last week of study		1	1
Terminal sacrifice	35	27	29
Missexed		1	
Animals examined microscopically	50	49	50
Alimentary System			
Intestine large, cecum	(50)	(49)	(50)
Intestine large, rectum	(50)	(46)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Liver	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Neoplastic nodule		1 (2%)	
Schwannoma malignant, metastatic, uncertain primary site		1 (2%)	
Mesentery	(2)	(2)	(2)
Pancreas	(50)	(49)	(50)
Salivary glands	(50)	(49)	(50)
Stomach, forestomach	(50)	(49)	(50)
Papilloma squamous			2 (4%)
Stomach, glandular	(50)	(49)	(50)
Cardiovascular System			
Heart	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Schwannoma malignant, metastatic, uncertain primary site		1 (2%)	
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(50)
Adenoma	1 (2%)	1 (2%)	
Adrenal gland, medulla	(48)	(49)	(49)
Pheochromocytoma benign	2 (4%)	1 (2%)	2 (4%)
Bilateral, pheochromocytoma benign			1 (2%)
Islets, pancreatic	(50)	(49)	(50)
Adenoma		1 (2%)	2 (4%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(49)	(50)
Pars distalis, adenoma	21 (42%)	20 (41%)	19 (38%)
Pars distalis, carcinoma	1 (2%)		
Thyroid gland	(50)	(48)	(49)
C-cell, adenoma	3 (6%)	3 (6%)	1 (2%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)
Follicular cell, adenoma		2 (4%)	
Follicular cell, carcinoma	1 (2%)	2 (4%)	
General Body System			
Tissue NOS	(1)		
Genital System			
Clitoral gland	(46)	(46)	(45)
Adenoma	1 (2%)	2 (4%)	3 (7%)
Carcinoma	1 (2%)	1 (2%)	3 (7%)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Ovary	(50)	(49)	(50)
Arrhenoblastoma NOS		1 (2%)	
Granulosa cell neoplasm benign		1 (2%)	
Luteoma		1 (2%)	
Uterus	(50)	(49)	(50)
Leiomyoma			1 (2%)
Leiomyosarcoma		1 (2%)	1 (2%)
Polyp stromal		1 (2%)	
Endometrium, polyp stromal	8 (16%)	11 (22%)	9 (18%)
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Lymph node	(44)	(48)	(49)
Mediastinal, follicular, carcinoma, metastatic, thyroid gland	1 (2%)		
Lymph node, mesenteric	(40)	(28)	(47)
Spleen	(50)	(49)	(50)
Capsule, fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Thymus	(48)	(43)	(48)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Integumentary System			
Mammary gland	(50)	(48)	(50)
Adenocarcinoma	3 (6%)		2 (4%)
Adenoma	1 (2%)		
Fibroadenoma	15 (30%)	5 (10%)	2 (4%)
Skin	(50)	(49)	(50)
Fibrosarcoma		2 (4%)	
Keratoacanthoma		2 (4%)	
Lip, squamous cell carcinoma	1 (2%)		
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(49)	(50)
Astrocytoma NOS		1 (2%)	
Ependymoma benign		1 (2%)	
Glioma benign		1 (2%)	
Respiratory System			
Lung	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)
Nose	(49)	(49)	(50)
Trachea	(50)	(49)	(50)
Fibrous histiocytoma, metastatic, uncertain primary site			1 (2%)
Special Senses System			
None			
Urinary System			
Kidney	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)
Renal tubule, adenoma			1 (2%)
Urinary bladder	(50)	(48)	(50)
Systemic Lesions			
Multiple organs[b]	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)
Leukemia monocytic			1 (2%)
Leukemia mononuclear	20 (40%)	11 (22%)	13 (26%)
Mesothelioma benign			1 (2%)
Mesothelioma malignant			1 (2%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Neoplasm Summary			
Total animals with primary neoplasms[c]	46	42	39
Total primary neoplasms	82	76	68
Total animals with benign neoplasms	35	37	31
Total benign neoplasms	54	55	45
Total animals with malignant neoplasms	24	15	21
Total malignant neoplasms	28	19	23
Total animals with metastatic neoplasms	1	1	1
Total metastatic neoplasms	1	2	7
Total animals with malignant neoplasms uncertain primary site		1	1
Total animals with neoplasms uncertain-benign or malignant		2	
Total uncertain neoplasms		2	

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

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

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

+: 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 Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 5	2 4 3	2 4 5	1 3 2	1 3 5	1 5 1	1 5 3	1 5 4	1 6 5	1 7 3	1 7 5	1 8 4	2 1 1	2 4 1	1 4 3	1 4 4	1 6 2	1 8 5	1 9 1	2 0 5	2 1 2	2 3 1	2 3 4	2 4 2	2 4 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+																							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Cardiovascular System																										
Blood vessel												+			+											15
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign		X																								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X			X	X					X	X					X	X	X	X	X		21
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X	X														X						3
C-cell, carcinoma													X													1
Follicular cell, carcinoma				X																						1

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

Number of Days on Study	5 3 1	5 7 2	5 7 3	5 7 6	5 9 0	6 1 4	6 2 1	6 4 1	6 4 3	6 5 5	6 5 6	6 5 7	6 5 9	6 6 6	6 9 8	7 2 9	7 2 9	7 2 9	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 8 3	1 9 5	2 1 4	1 4 1	2 3 2	2 2 4	1 3 3	1 9 4	1 6 1	1 4 2	1 9 3	1 9 2	2 2 3	1 7 2	1 5 2	1 7 4	1 0 1	2 0 4	2 0 4	1 3 1	1 5 5	1 6 4	1 8 2	2 1 3	2 2 5	2 3 3
General Body System																										
Tissue NOS										+																
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Adenoma																										
Carcinoma																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal						X			X										X		X	X				
Vagina																	+									
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Mediastinal, follicular, carcinoma, metastatic, thyroid gland																										
Lymph node, mesenteric	+	+		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X																	X					X	
Adenoma																										
Fibroadenoma				X			X	X		X		X		X		X			X		X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lip, squamous cell carcinoma															X											
Sebaceous gland, adenoma																										
Subcutaneous tissue, fibroma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+							

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 5	2 4 3	2 4 5	1 3 2	1 3 5	1 5 1	1 5 3	1 5 4	1 6 5	1 7 3	1 7 5	1 8 4	2 1 1	2 4 1	1 4 3	1 4 4	1 6 2	1 8 5	1 9 1	2 0 5	2 1 2	2 3 1	2 3 4	2 4 2	2 4 4	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Adenoma						X																				1
Carcinoma																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal						X		X										X								8
Vagina											+															2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	44
Mediastinal, follicular, carcinoma, metastatic, thyroid gland				X																						1
Lymph node, mesenteric	+	+	M	+			+	+		M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										3
Adenoma																				X						1
Fibroadenoma					X							X			X		X			X			X			15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lip, squamous cell carcinoma																										1
Sebaceous gland, adenoma								X																		1
Subcutaneous tissue, fibroma						X																				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle												+														2

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

Number of Days on Study	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	3	7	7	7	9	1	2	4	4	5	5	5	5	6	9	2	2	2	3	3	3	3	3	3	3	
	1	2	3	6	0	4	1	1	3	5	6	7	9	6	8	9	9	9	2	2	2	2	2	2	2	
Carcass ID Number	1	1	2	1	2	2	1	1	1	1	1	1	2	1	1	1	2	2	1	1	1	1	2	2	2	
	8	9	1	4	3	2	3	9	6	4	9	9	2	7	5	7	0	0	3	5	6	8	1	2	3	
	3	5	4	1	2	4	3	4	1	2	3	2	3	2	2	4	1	4	1	5	4	2	3	5	3	
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye												+		+	+		+									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X	X	X		X	X		X	X	X	X		X		X		X			X				X		

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 3 5	2 4 3	2 4 5	1 3 2	1 3 5	1 5 1	1 5 3	1 5 4	1 6 5	1 7 3	1 7 5	1 8 4	2 1 1	2 4 1	1 4 3	1 4 4	1 6 2	1 8 5	1 9 1	2 0 5	2 1 2	2 3 1	2 3 4	2 4 2	2 4 4	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+																				5
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X		X	X	X			X					X							20

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg

Number of Days on Study	0 8 4	2 7 7	2 8 5	4 3 7	5 2 3	5 5 2	5 6 5	5 7 1	5 8 2	5 9 5	6 0 1	6 0 9	6 1 4	6 2 9	6 4 7	6 5 6	6 8 4	6 8 7	7 0 8	7 1 7	7 1 7	7 2 9	7 2 9	7 3 1
Carcass ID Number	4 4 1	4 6 1	4 7 1	4 5 5	4 3 1	4 6 3	4 7 5	4 2 3	4 2 1	3 9 5	4 0 5	4 1 4	3 9 2	4 8 2	4 3 4	4 5 1	4 7 2	4 4 2	4 5 2	3 7 3	4 7 4	4 4 3	4 8 3	4 6 2
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																								
Schwannoma malignant, metastatic, uncertain primary site																				X				
Mesentery																		+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+																		
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, uncertain primary site																				X				
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X			X					X			X	X			X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	3 9 3	4 0 2	4 0 3	4 1 5	4 2 2	4 2 5	4 3 2	4 8 1	3 7 1	3 7 2	3 8 5	3 9 4	4 2 4	4 4 4	4 6 5	4 7 4	4 8 3	4 8 5	3 7 4	3 9 1	4 0 4	4 1 1	4 1 3	4 3 5	4 4 4	4 5 3	**Total Tissues/ Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule		X																									1
Schwannoma malignant, metastatic, uncertain primary site																											1
Mesentery																+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																											1
Cardiovascular System																											
Blood vessel																											18
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, uncertain primary site																											1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X																							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X		X		X	X		X	X			X	X	X		X		X		X	X			20

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	0 8 4	2 7 7	2 8 5	4 3 7	5 2 3	5 5 2	5 6 5	5 7 1	5 8 2	5 9 5	6 0 1	6 0 9	6 1 4	6 2 9	6 4 7	6 5 6	6 8 4	6 8 7	7 0 8	7 1 7	7 1 7	7 2 9	7 2 9	7 3 1
Carcass ID Number	4 4 1	4 6 1	4 7 1	4 5 5	4 3 1	4 6 3	4 7 5	4 2 3	4 2 1	3 9 5	4 0 5	4 1 4	3 9 2	4 8 2	4 3 4	4 5 1	4 7 2	4 4 2	4 5 2	3 7 3	4 7 4	4 4 3	4 8 3	4 6 2
Endocrine System (continued)																								
Thyroid gland	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X										
C-cell, carcinoma																	X							
Follicular cell, adenoma											X													
Follicular cell, carcinoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																	X		X					
Carcinoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Arrhenoblastoma NOS																								
Granulosa cell tumor benign																							X	
Luteoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																								
Polyp stromal					X																			
Endometrium, polyp stromal																				X		X		
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	I	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X		X				
Keratoacanthoma																								
Subcutaneous tissue, fibroma												X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 9 3	4 0 2	4 0 3	4 1 5	4 2 2	4 2 5	4 3 2	4 8 1	3 7 1	3 7 2	3 8 5	3 9 4	4 2 4	4 4 5	4 6 4	4 7 3	4 8 5	3 7 4	3 9 1	4 0 4	4 1 1	4 1 3	4 3 5	4 4 4	4 5 3	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma					X					X																3
C-cell, carcinoma															X											2
Follicular cell, adenoma			X																							2
Follicular cell, carcinoma																				X	X					2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Adenoma																										2
Carcinoma																					X					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Arrhenoblastoma NOS									X																	1
Granulosa cell tumor benign																										1
Luteoma									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma												X														1
Polyp stromal																										1
Endometrium, polyp stromal	X				X	X								X				X	X		X			X	X	11
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+						+	+	+						+	M	+	+	+				28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma					X			X	X										X							5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										2
Keratoacanthoma																	X					X				2
Subcutaneous tissue, fibroma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	0	2	2	4	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7
	8	7	8	3	2	5	6	7	8	9	0	0	1	2	4	5	8	8	0	1	1	2	2	3
	4	7	5	7	3	2	5	1	2	5	1	9	4	9	7	6	4	7	8	7	7	9	9	1
Carcass ID Number	4	4	4	4	4	4	4	4	4	3	4	4	3	4	4	4	4	4	4	3	4	4	4	4
	4	6	7	5	3	6	7	2	2	9	0	1	9	8	3	5	7	4	5	7	7	4	8	6
	1	1	1	5	1	3	5	3	1	5	5	4	2	2	4	1	2	2	2	3	4	3	3	2
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																								
Ependymoma benign							X																	
Glioma benign								X																
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X										X		X		X			X	X					X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 2.5 mg/kg (continued)

Number of Days on Study	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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	3 9 3	4 0 2	4 0 3	4 1 5	4 2 2	4 2 5	4 3 2	4 8 1	3 7 1	3 7 2	3 8 5	3 9 4	4 2 4	4 4 5	4 6 4	4 7 3	4 8 5	3 7 4	3 9 1	4 0 4	4 1 1	4 1 3	4 3 5	4 4 4	4 5 3	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma NOS																				X						1
Ependymoma benign																										1
Glioma benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye				+													+							+		3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear							X	X							X						X					11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg

Number of Days on Study	0 4 2	0 8 7	1 0 6	3 1 3	4 2 8	5 1 5	5 1 8	5 8 0	5 8 1	5 8 6	5 9 3	6 2 3	6 2 6	6 2 9	6 3 1	6 3 6	6 6 5	6 9 2	6 9 2	7 0 0	7 2 9	7 2 9	7 3 0	7 3 2	7 3 2
Carcass ID Number	6 1 1	6 7 1	7 2 1	6 3 1	7 1 4	6 9 1	6 9 5	6 8 3	6 6 2	7 0 2	6 7 3	6 6 5	7 6 2	6 2 2	6 2 5	7 7 5	7 0 4	6 2 2	7 1 1	7 1 2	6 2 3	6 4 5	6 8 2	7 2 4	6 1 3	6 2 4
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site														X												
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site														X												
Mesentery																+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site														X												
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X										
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 4 4	6 6 1	6 7 4	7 0 1	7 0 3	6 1 2	6 5 3	6 6 3	6 6 4	6 7 2	6 8 1	6 9 2	6 9 3	7 2 5	6 1 4	6 2 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 5 1	6 5 4	6 6 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Mesentery			+																							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous													X			X										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										19
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X																								2
Bilateral, pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X				X			2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0 4 2	0 8 7	1 0 6	3 1 3	4 2 8	5 1 5	5 1 8	5 1 0	5 8 1	5 8 6	5 8 3	6 9 3	6 2 3	6 2 6	6 2 9	6 3 1	6 3 6	6 6 5	6 9 2	6 9 2	7 0 0	7 2 9	7 2 9	7 3 0	7 3 2	7 3 2
Carcass ID Number	6 1 1	6 7 1	7 2 1	6 3 1	7 1 4	6 9 1	6 9 5	6 8 3	6 6 2	7 0 2	6 7 3	6 6 5	7 2 5	6 2 2	6 2 5	7 7 5	7 0 4	6 2 2	7 1 1	7 1 2	6 2 3	6 4 5	6 8 2	7 2 4	6 1 3	6 2 4
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X			X			X	X			X	X	X	X			X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								X		
C-cell, carcinoma																										
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma															X											
Carcinoma																X										
Fibrous histiocytoma, metastatic, uncertain primary site														X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																										
Leiomyosarcoma																										
Endometrium, polyp stromal																									X	
Vagina																			+							
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrous histiocytoma, metastatic, uncertain primary site															X											
Thymus	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site															X											
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Fibroadenoma																						X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma															X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 4 4	6 6 1	6 7 4	7 0 1	7 0 3	6 1 2	6 5 3	6 6 3	6 6 4	6 7 2	6 8 1	6 9 2	6 9 3	7 2 5	6 1 4	6 2 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 5 1	6 5 4	6 9 4	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X	X	X							X			X		X		X	X	X			19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
C-cell, adenoma																										1
C-cell, carcinoma							X																			1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	45
Adenoma				X						X																3
Carcinoma																		X							X	3
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma														X												1
Leiomyosarcoma																								X		1
Endometrium, polyp stromal	X	X										X		X			X	X			X		X			9
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrous histiocytoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrous histiocytoma, metastatic, uncertain primary site																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																						X	X			2
Fibroadenoma			X																							2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0	0	1	3	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	4	8	0	1	2	1	1	8	8	8	9	2	2	2	3	3	6	9	9	0	2	2	3	3	3
	2	7	6	3	8	5	8	0	1	6	3	3	6	9	1	6	5	2	2	0	9	9	0	2	2
Carcass ID Number	6	6	7	6	7	6	6	6	6	7	6	6	7	6	6	7	6	7	7	6	6	6	7	6	6
	1	7	2	3	1	9	9	8	6	0	7	6	2	2	7	0	2	1	1	2	4	8	2	1	2
	1	1	1	1	4	1	5	3	2	2	3	5	2	5	5	4	2	1	2	3	5	2	4	3	4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, uncertain primary site														X											
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Renal tubule, adenoma																		X							
Ureter																								+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Leukemia monocytic																					X				
Leukemia mononuclear						X				X	X		X						X	X		X	X		
Mesothelioma benign															X										
Mesothelioma malignant															X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 3 5	6 4 4	6 6 1	6 7 4	7 0 1	7 0 3	6 1 2	6 5 3	6 6 3	6 6 4	6 7 2	6 8 1	6 9 2	6 9 3	7 2 5	6 1 4	6 2 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 5 1	6 5 4	6 9 4	**Total Tissues/ Tumors**
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, uncertain primary site																									1
Special Senses System																									
Eye			+																+						2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Renal tubule, adenoma																									1
Ureter																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Leukemia monocytic																									1
Leukemia mononuclear		X					X		X	X												X			13
Mesothelioma benign																									1
Mesothelioma malignant																									1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	2.5 mg/kg	5 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	2/48 (4%)	1/49 (2%)	3/49 (6%)
Adjusted rates[b]	5.9%	3.3%	9.6%
Terminal rates[c]	2/34 (6%)	0/28 (0%)	2/29 (7%)
First incidence (days)	729 (T)	717	636
Life table tests[d]	P=0.337	P=0.563N	P=0.424
Logistic regression tests[d]	P=0.352	P=0.546N	P=0.447
Cochran-Armitage test[d]	P=0.407		
Fisher exact test[d]		P=0.492N	P=0.510
Clitoral Gland: Adenoma			
Overall rates	1/46 (2%)	2/46 (4%)	3/45 (7%)
Adjusted rates	3.1%	6.2%	9.7%
Terminal rates	1/32 (3%)	0/27 (0%)	2/28 (7%)
First incidence (days)	729 (T)	684	631
Life table tests	P=0.188	P=0.457	P=0.256
Logistic regression tests	P=0.190	P=0.467	P=0.265
Cochran-Armitage test	P=0.215		
Fisher exact test		P=0.500	P=0.300
Clitoral Gland: Carcinoma			
Overall rates	1/46 (2%)	1/46 (2%)	3/45 (7%)
Adjusted rates	3.1%	3.7%	9.8%
Terminal rates	1/32 (3%)	1/27 (4%)	2/28 (7%)
First incidence (days)	729 (T)	729 (T)	636
Life table tests	P=0.168	P=0.724	P=0.254
Logistic regression tests	P=0.172	P=0.724	P=0.264
Cochran-Armitage test	P=0.195		
Fisher exact test		P=0.753N	P=0.300
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	2/46 (4%)	3/46 (7%)	6/45 (13%)
Adjusted rates	6.3%	9.6%	19.0%
Terminal rates	2/32 (6%)	1/27 (4%)	4/28 (14%)
First incidence (days)	729 (T)	684	631
Life table tests	P=0.066	P=0.436	P=0.094
Logistic regression tests	P=0.065	P=0.453	P=0.099
Cochran-Armitage test	P=0.084		
Fisher exact test		P=0.500	P=0.126
Mammary Gland: Adenocarcinoma			
Overall rates	3/50 (6%)	0/49 (0%)	2/50 (4%)
Adjusted rates	7.7%	0.0%	6.7%
Terminal rates	2/35 (6%)	0/28 (0%)	2/30 (7%)
First incidence (days)	573	–[e]	729 (T)
Life table tests	P=0.447N	P=0.161N	P=0.566N
Logistic regression tests	P=0.426N	P=0.119N	P=0.542N
Cochran-Armitage test	P=0.391N		
Fisher exact test		P=0.125N	P=0.500N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Mammary Gland: Fibroadenoma			
Overall rates	15/50 (30%)	5/49 (10%)	2/50 (4%)
Adjusted rates	35.8%	16.7%	6.7%
Terminal rates	9/35 (26%)	4/28 (14%)	2/30 (7%)
First incidence (days)	576	629	729 (T)
Life table tests	P=0.001N	P=0.047N	P=0.003N
Logistic regression tests	P<0.001N	P=0.020N	P=0.001N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.013N	P<0.001N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall rates	18/50 (36%)	5/49 (10%)	4/50 (8%)
Adjusted rates	42.0%	16.7%	13.3%
Terminal rates	11/35 (31%)	4/28 (14%)	4/30 (13%)
First incidence (days)	573	629	729 (T)
Life table tests	P=0.001N	P=0.014N	P=0.004N
Logistic regression tests	P<0.001N	P=0.004N	P=0.002N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.002N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	21/50 (42%)	20/49 (41%)	19/50 (38%)
Adjusted rates	51.9%	59.9%	49.7%
Terminal rates	16/35 (46%)	15/28 (54%)	11/30 (37%)
First incidence (days)	573	571	580
Life table tests	P=0.458	P=0.331	P=0.510
Logistic regression tests	P=0.514	P=0.448	P=0.577
Cochran-Armitage test	P=0.380N		
Fisher exact test		P=0.534N	P=0.419N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	22/50 (44%)	20/49 (41%)	19/50 (38%)
Adjusted rates	54.4%	59.9%	49.7%
Terminal rates	17/35 (49%)	15/28 (54%)	11/30 (37%)
First incidence (days)	573	571	580
Life table tests	P=0.529	P=0.397	P=0.570N
Logistic regression tests	P=0.491N	P=0.525	P=0.514N
Cochran-Armitage test	P=0.306N		
Fisher exact test		P=0.453N	P=0.342N
Thyroid Gland (C-cell): Adenoma			
Overall rates	3/50 (6%)	3/48 (6%)	1/49 (2%)
Adjusted rates	8.6%	9.7%	3.4%
Terminal rates	3/35 (9%)	2/28 (7%)	1/29 (3%)
First incidence (days)	729 (T)	629	729 (T)
Life table tests	P=0.311N	P=0.560	P=0.374N
Logistic regression tests	P=0.298N	P=0.595	P=0.374N
Cochran-Armitage test	P=0.247N		
Fisher exact test		P=0.641	P=0.316N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	4/50 (8%)	5/48 (10%)	2/49 (4%)
Adjusted rates	11.4%	15.8%	6.9%
Terminal rates	4/35 (11%)	3/28 (11%)	2/29 (7%)
First incidence (days)	729 (T)	629	729 (T)
Life table tests	P=0.377N	P=0.376	P=0.426N
Logistic regression tests	P=0.364N	P=0.409	P=0.426N
Cochran-Armitage test	P=0.293N		
Fisher exact test		P=0.474	P=0.349N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	1/50 (2%)	4/48 (8%)	0/49 (0%)
Adjusted rates	2.9%	13.0%	0.0%
Terminal rates	1/35 (3%)	3/28 (11%)	0/29 (0%)
First incidence (days)	729 (T)	601	–
Life table tests	P=0.459N	P=0.124	P=0.538N
Logistic regression tests	P=0.440N	P=0.142	P=0.538N
Cochran-Armitage test	P=0.398N		
Fisher exact test		P=0.168	P=0.505N
Uterus: Stromal Polyp			
Overall rates	8/50 (16%)	12/49 (24%)	9/50 (18%)
Adjusted rates	20.9%	39.2%	30.0%
Terminal rates	6/35 (17%)	10/28 (36%)	9/30 (30%)
First incidence (days)	614	523	729 (T)
Life table tests	P=0.300	P=0.101	P=0.359
Logistic regression tests	P=0.323	P=0.138	P=0.380
Cochran-Armitage test	P=0.450		
Fisher exact test		P=0.212	P=0.500
All Organs: Monocytic or Mononuclear Cell Leukemia			
Overall rates	20/50 (40%)	11/49 (22%)	14/50 (28%)
Adjusted rates	42.7%	30.5%	37.7%
Terminal rates	9/35 (26%)	5/28 (18%)	8/30 (27%)
First incidence (days)	531	84	515
Life table tests	P=0.268N	P=0.164N	P=0.323N
Logistic regression tests	P=0.111N	P=0.024N	P=0.154N
Cochran-Armitage test	P=0.115N		
Fisher exact test		P=0.047N	P=0.146N
All Organs: Benign Neoplasms			
Overall rates	35/50 (70%)	37/49 (76%)	31/50 (62%)
Adjusted rates	77.5%	92.4%	79.4%
Terminal rates	25/35 (71%)	25/28 (89%)	22/30 (73%)
First incidence (days)	573	523	580
Life table tests	P=0.443	P=0.073	P=0.507
Logistic regression tests	P=0.547	P=0.110	P=0.566N
Cochran-Armitage test	P=0.224N		
Fisher exact test		P=0.349	P=0.263N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	2.5 mg/kg	5 mg/kg
All Organs: Malignant Neoplasms			
Overall rates	24/50 (48%)	15/49 (31%)	21/50 (42%)
Adjusted rates	51.5%	40.5%	53.1%
Terminal rates	13/35 (37%)	7/28 (25%)	12/30 (40%)
First incidence (days)	531	84	515
Life table tests	P=0.530	P=0.222N	P=0.541
Logistic regression tests	P=0.351N	P=0.045N	P=0.410N
Cochran-Armitage test	P=0.305N		
Fisher exact test		P=0.059N	P=0.344N
All Organs: Benign or Malignant Neoplasms			
Overall rates	46/50 (92%)	42/49 (86%)	39/50 (78%)
Adjusted rates	92.0%	97.7%	90.7%
Terminal rates	31/35 (89%)	27/28 (96%)	26/30 (87%)
First incidence (days)	531	84	515
Life table tests	P=0.498N	P=0.265	P=0.517N
Logistic regression tests	P=0.180N	P=0.510N	P=0.242N
Cochran-Armitage test	P=0.033N		
Fisher exact test		P=0.251N	P=0.045N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, 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 neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column 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 neoplasms 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 neoplasms in animal group

TABLE B4a
Historical Incidence of Renal Tubule Neoplasms in Female F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/265 (0.0%)	0/265 (0.0%)	0/265 (0.0%)

[a] Data as of 17 September 1990

TABLE B4b
Historical Incidence of Forestomach Neoplasms in Female F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Squamous Cell Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/265 (0.0%)	0/265 (0.0%)	0/265 (0.0%)

[a] Data as of 17 September 1990

TABLE B4c
Historical Incidence of Mammary Gland Neoplasms in Female F344 Rats Receiving Water by Gavage[a]

Study	Incidence in Controls			
	Fibroadenoma	Adenoma	Adenocarcinoma	Carcinoma
Historical Incidence at International Research and Development Corporation				
Resorcinol	25/50	1/50	1/50	0/50
Overall Historical Incidence				
Total	101/265 (38.1%)	4/265 (1.5%)	6/265 (2.3%)	1/265 (0.4%)
Standard deviation	14.8%	1.3%	1.8%	0.9%
Range	16%-53%	0%-3%	0%-5%	0%-2%

[a] Data as of 17 September 1990

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	2.5 mg/kg	5 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	14	14	9
Natural deaths	1	7	11
Survivors			
Died last week of study		1	1
Terminal sacrifice	35	27	29
Missexed		1	
Animals examined microscopically	50	49	50
Alimentary System			
Intestine large, cecum	(50)	(49)	(50)
Inflammation, chronic			2 (4%)
Intestine large, colon	(50)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)
Parasite metazoan	1 (2%)	1 (2%)	2 (4%)
Intestine large, rectum	(50)	(46)	(50)
Parasite metazoan	2 (4%)	2 (4%)	2 (4%)
Intestine small, duodenum	(50)	(49)	(50)
Autolysis		1 (2%)	3 (6%)
Intestine small, ileum	(50)	(49)	(50)
Autolysis		1 (2%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)
Intestine small, jejunum	(50)	(49)	(50)
Autolysis		2 (4%)	4 (8%)
Liver	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Basophilic focus, multiple	27 (54%)	28 (57%)	32 (64%)
Clear cell focus			9 (18%)
Congestion		4 (8%)	1 (2%)
Cytoplasmic alteration, focal	3 (6%)	4 (8%)	1 (2%)
Degeneration, fatty		1 (2%)	2 (4%)
Ectasia, focal			1 (2%)
Eosinophilic focus			1 (2%)
Hematopoietic cell proliferation		1 (2%)	
Hemorrhage			1 (2%)
Hepatodiaphragmatic nodule	8 (16%)	4 (8%)	8 (16%)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, granulomatous	18 (36%)	23 (47%)	17 (34%)
Mixed cell focus			1 (2%)
Mixed cell focus, multiple			1 (2%)
Necrosis, acute	1 (2%)	1 (2%)	2 (4%)
Vacuolization cytoplasmic, focal	2 (4%)	3 (6%)	3 (6%)
Bile duct, hyperplasia	1 (2%)	4 (8%)	3 (6%)
Hepatocyte, hyperplasia		1 (2%)	
Mesentery	(2)	(2)	(2)
Fat, necrosis, focal	2 (100%)	2 (100%)	1 (50%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Alimentary System (continued)			
Pancreas	(50)	(49)	(50)
Atrophy, focal	20 (40%)	17 (35%)	20 (40%)
Autolysis		1 (2%)	1 (2%)
Cytoplasmic alteration, focal			1 (2%)
Ectopic liver			1 (2%)
Infiltration cellular, lymphocyte, focal			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Salivary glands	(50)	(49)	(50)
Cytoplasmic alteration, focal			2 (4%)
Hemorrhage, focal	1 (2%)		
Stomach, forestomach	(50)	(49)	(50)
Edema	1 (2%)		
Hyperplasia	5 (10%)	5 (10%)	20 (40%)
Inflammation, acute	2 (4%)	1 (2%)	2 (4%)
Ulcer	1 (2%)		1 (2%)
Stomach, glandular	(50)	(49)	(50)
Autolysis		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Necrosis	3 (6%)	1 (2%)	4 (8%)
Tongue	(1)		
Hemorrhage, focal	1 (100%)		
Tooth		(1)	
Inflammation, acute		1 (100%)	
Cardiovascular System			
Blood vessel	(15)	(18)	(19)
Aorta, inflammation, chronic	1 (7%)		
Mesenteric artery, inflammation, chronic	1 (7%)		
Heart	(50)	(49)	(50)
Inflammation, chronic	31 (62%)	38 (78%)	39 (78%)
Atrium left, thrombus		4 (8%)	2 (4%)
Coronary artery, inflammation, chronic	1 (2%)		
Endocardium, fibrosis	1 (2%)		
Epicardium, inflammation, chronic	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(50)
Accessory adrenal cortical nodule	1 (2%)		
Angiectasis		5 (10%)	3 (6%)
Congestion		5 (10%)	
Degeneration, fatty	1 (2%)	2 (4%)	
Hyperplasia, focal	5 (10%)	11 (22%)	11 (22%)
Hypertrophy, focal	3 (6%)	3 (6%)	4 (8%)
Necrosis, focal		1 (2%)	
Vacuolization cytoplasmic, focal	10 (20%)	7 (14%)	4 (8%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(48)	(49)	(49)
Cyst	1 (2%)		
Hyperplasia, focal	4 (8%)	8 (16%)	5 (10%)
Bilateral, hyperplasia, focal	1 (2%)		
Islets, pancreatic	(50)	(49)	(50)
Hyperplasia, focal	2 (4%)		2 (4%)
Parathyroid gland	(47)	(49)	(45)
Hyperplasia, focal	1 (2%)	1 (2%)	
Pituitary gland	(50)	(49)	(50)
Pars distalis, angiectasis	8 (16%)	7 (14%)	2 (4%)
Pars distalis, cyst	13 (26%)	16 (33%)	5 (10%)
Pars distalis, ectasia	1 (2%)	1 (2%)	
Pars distalis, hemorrhage		1 (2%)	
Pars distalis, hyperplasia	10 (20%)	10 (20%)	9 (18%)
Pars distalis, hypertrophy		1 (2%)	3 (6%)
Pars intermedia, hyperplasia		1 (2%)	
Thyroid gland	(50)	(48)	(49)
Ultimobranchial cyst		1 (2%)	
C-cell, hyperplasia	15 (30%)	3 (6%)	5 (10%)
Follicle, cyst		1 (2%)	4 (8%)
Follicular cell, hyperplasia			1 (2%)
General Body System			
None			
Genital System			
Clitoral gland	(46)	(46)	(45)
Hyperplasia		1 (2%)	
Inflammation, acute		2 (4%)	
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Duct, ectasia	2 (4%)	2 (4%)	2 (4%)
Ovary	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Bilateral, periovarian tissue, cyst	1 (2%)		
Follicle, cyst	1 (2%)	3 (6%)	3 (6%)
Parovarian tissue, cyst	1 (2%)		
Uterus	(50)	(49)	(50)
Cyst			1 (2%)
Dilatation		1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia, cystic	1 (2%)		
Inflammation, acute		1 (2%)	
Cervix, cyst			1 (2%)
Endometrium, cyst	1 (2%)	2 (4%)	4 (8%)
Endometrium, hyperplasia, cystic	3 (6%)	2 (4%)	7 (14%)
Vagina	(2)		(1)
Inflammation, acute			1 (100%)

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Hematopoietic System			
Bone marrow	(50)	(49)	(50)
Hypoplasia		1 (2%)	
Myelofibrosis	4 (8%)	1 (2%)	
Myeloid cell, hyperplasia	1 (2%)	1 (2%)	
Lymph node	(44)	(48)	(49)
Inguinal, hyperplasia, lymphoid			1 (2%)
Mandibular, hyperplasia, lymphoid	1 (2%)		
Mandibular, hyperplasia, plasma cell		1 (2%)	
Mediastinal, congestion			1 (2%)
Mediastinal, hemorrhage		1 (2%)	
Lymph node, mesenteric	(40)	(28)	(47)
Ectasia	2 (5%)		
Hyperplasia, plasma cell	1 (3%)		
Hyperplasia, RE cell			2 (4%)
Inflammation	1 (3%)		
Spleen	(50)	(49)	(50)
Hematopoietic cell proliferation granulocytic	1 (2%)		2 (4%)
Capsule, fibrosis, focal	1 (2%)		
Thymus	(48)	(43)	(48)
Congestion	1 (2%)		
Cyst		1 (2%)	3 (6%)
Hemorrhage			1 (2%)
Integumentary System			
Mammary gland	(50)	(48)	(50)
Cyst	1 (2%)		
Galactocele	2 (4%)	2 (4%)	1 (2%)
Hyperplasia	4 (8%)	3 (6%)	2 (4%)
Inflammation, acute		1 (2%)	1 (2%)
Duct, ectasia	11 (22%)	8 (17%)	7 (14%)
Skin	(50)	(49)	(50)
Inflammation, acute		1 (2%)	
Musculoskeletal System			
Bone	(50)	(49)	(50)
Inflammation, acute		1 (2%)	
Osteopetrosis	2 (4%)	1 (2%)	3 (6%)
Skeletal muscle	(2)		
Inflammation, chronic	2 (100%)		
Nervous System			
Brain	(50)	(49)	(50)
Demyelination, focal		1 (2%)	
Hemorrhage		1 (2%)	
Hydrocephalus		1 (2%)	1 (2%)
Inflammation, chronic, focal			1 (2%)
White matter, vacuolization cytoplasmic		1 (2%)	

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Respiratory System			
Lung	(50)	(49)	(50)
Congestion	7 (14%)	16 (33%)	18 (36%)
Ectopic tissue		1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic	3 (6%)	1 (2%)	4 (8%)
Inflammation, focal		1 (2%)	
Inflammation, granulomatous	2 (4%)		1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	4 (8%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	2 (4%)	2 (4%)	4 (8%)
Perivascular, infiltration cellular, lymphocyte		1 (2%)	2 (4%)
Nose	(49)	(49)	(50)
Autolysis	1 (2%)		3 (6%)
Foreign body			4 (8%)
Fungus		3 (6%)	2 (4%)
Mucosa, cyst	1 (2%)		
Mucosa, inflammation, acute		1 (2%)	3 (6%)
Mucosa, inflammation, chronic active		4 (8%)	12 (24%)
Mucosa, mineralization, focal		1 (2%)	
Nasolacrimal duct, inflammation, acute	2 (4%)	2 (4%)	
Nasolacrimal duct, inflammation, chronic	1 (2%)		1 (2%)
Respiratory epithelium, degeneration		1 (2%)	
Respiratory epithelium, hyperplasia			1 (2%)
Respiratory epithelium, metaplasia, squamous		1 (2%)	1 (2%)
Trachea	(50)	(49)	(50)
Inflammation, acute			2 (4%)
Inflammation, granulomatous		1 (2%)	
Special Senses System			
Eye	(5)	(3)	(2)
Hemorrhage	2 (40%)	1 (33%)	
Lens, cataract	3 (60%)	3 (100%)	2 (100%)
Lens, degeneration	1 (20%)		
Retina, degeneration	4 (80%)	2 (67%)	1 (50%)
Sclera, degeneration	1 (20%)		
Urinary System			
Kidney	(50)	(49)	(50)
Autolysis	1 (2%)		1 (2%)
Congestion		3 (6%)	
Cyst			2 (4%)
Degeneration, hyaline		1 (2%)	
Hemorrhage, focal			1 (2%)
Karyomegaly		4 (8%)	
Mineralization		2 (4%)	
Nephropathy	49 (98%)	43 (88%)	41 (82%)
Pigmentation	3 (6%)	1 (2%)	3 (6%)
Renal tubule, hyperplasia			2 (4%)
Renal tubule, hyperplasia, oncocytic		1 (2%)	
Renal tubule, hypertrophy		1 (2%)	
Urinary bladder	(50)	(48)	(50)
Hemorrhage			1 (2%)
Transitional epithelium, hyperplasia		1 (2%)	

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF MERCURIC CHLORIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	6	4	11
Natural deaths	8	10	8
Survivors			
Died last week of study	1		
Terminal sacrifice	35	36	31
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(49)	(48)	(49)
Intestine large, rectum	(47)	(47)	(49)
Adenocarcinoma		1 (2%)	
Intestine small, duodenum	(46)	(43)	(45)
Polyp adenomatous	1 (2%)		
Intestine small, ileum	(44)	(43)	(45)
Intestine small, jejunum	(48)	(43)	(45)
Liver	(50)	(50)	(50)
Hemangioma	1 (2%)	1 (2%)	
Hepatocellular carcinoma	2 (4%)	2 (4%)	6 (12%)
Hepatocellular carcinoma, multiple	3 (6%)	1 (2%)	
Hepatocellular adenoma	1 (2%)		1 (2%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	
Mesentery	(3)		(2)
Pancreas	(50)	(46)	(49)
Hemangioma			1 (2%)
Salivary glands	(50)	(48)	(49)
Stomach, forestomach	(50)	(48)	(50)
Papilloma squamous			1 (2%)
Squamous cell carcinoma		1 (2%)	
Stomach, glandular	(49)	(47)	(49)
Tooth	(3)	(2)	(3)
Cardiovascular System			
Blood vessel	(10)	(14)	(18)
Vena cava, fibrosarcoma, metastatic, skin			1 (6%)
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(49)
Adenoma	1 (2%)		
Subcapsular, adenoma	1 (2%)		1 (2%)
Adrenal gland, medulla	(45)	(50)	(49)
Pheochromocytoma benign	1 (2%)	1 (2%)	

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

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System (continued)			
Pituitary gland	(48)	(47)	(47)
Adenoma	1 (2%)		
Pars intermedia, adenoma	2 (4%)		1 (2%)
Thyroid gland	(49)	(47)	(49)
Follicular cell, adenoma		1 (2%)	
Follicular cell, carcinoma	1 (2%)		
General Body System			
Tissue NOS		(1)	(1)
Mediastinum, fibrosarcoma, metastatic, skin			1 (100%)
Genital System			
Penis	(4)	(2)	(6)
Prostate	(46)	(49)	(46)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(44)	(48)	(43)
Spleen	(50)	(49)	(49)
Thymus	(26)	(34)	(27)
Integumentary System			
Skin	(50)	(50)	(50)
Fibroma		1 (2%)	
Fibrosarcoma	2 (4%)	3 (6%)	
Fibrosarcoma, metastatic			1 (2%)
Musculoskeletal System			
Skeletal muscle	(2)	(2)	
Fibrosarcoma		1 (50%)	
Nervous System			
None			
Respiratory System			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	5 (10%)	3 (6%)
Alveolar/bronchiolar adenoma, multiple		3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)		2 (4%)
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	1 (2%)
Nose	(50)	(50)	(50)
Trachea	(50)	(50)	(50)

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

	Vehicle Control	5 mg/kg	10 mg/kg
Special Senses System			
Harderian gland	(1)	(3)	(1)
Adenoma		3 (100%)	1 (100%)
Adenoma, multiple	1 (100%)		
Urinary System			
Kidney	(50)	(50)	(49)
Renal tubule, adenocarcinoma			1 (2%)
Renal tubule, adenoma			2 (4%)
Urinary bladder	(45)	(48)	(46)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant mixed	7 (14%)	2 (4%)	3 (6%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	28	20	17
Total primary neoplasms	37	27	24
Total animals with benign neoplasms	13	15	10
Total benign neoplasms	17	16	12
Total animals with malignant neoplasms	20	10	11
Total malignant neoplasms	20	11	12
Total animals with metastatic neoplasms	2	2	2
Total metastatic neoplasms	2	2	5
Total animals with malignant neoplasms uncertain primary site		1	

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control

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

+: 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 Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 4 5	0 4 4	0 9 5	1 0 5	1 1 2	1 2 1	0 1 4	0 2 3	0 2 4	0 4 2	0 5 2	0 5 3	0 9 1	1 0 2	1 2 4	0 1 3	0 1 5	0 6 3	0 8 2	0 8 5	0 9 2	1 1 3	1 1 4	1 2 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	46
Polyp adenomatous					X																					1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatocellular carcinoma												X							X							2
Hepatocellular carcinoma, multiple																						X		X		3
Hepatocellular adenoma																				X						1
Hepatocellular adenoma, multiple																										1
Mesentery																					+					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										3
Cardiovascular System																										
Blood vessel																										10
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Subcapsular, adenoma	X																									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	45
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	0 6 2	0 8 5	0 9 6	0 9 9	1 0 5	1 1 2	1 2 9	1 9 7	4 5 7	5 9 5	6 3 7	6 9 5	6 9 9	7 0 1	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	0 6 1	1 0 1	0 3 1	0 2 1	0 6 2	1 1 1	0 8 1	0 4 1	0 6 4	0 2 5	0 7 2	1 0 3	0 8 3	1 1 5	0 3 2	0 3 5	0 4 4	0 6 5	0 7 3	0 7 5	0 8 4	0 9 4	1 2 3	0 1 2	0 3 4
Endocrine System (continued)																									
Parathyroid gland	M	M	+	M	+	M	M	+	M	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																	X								
Pars intermedia, adenoma															X										
Thyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland										+		+		+											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+			+																					
Preputial gland					+		+						+	+	+			+	+	+			+		
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle			+	+	+				+	+		+		+											
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	M	M	M	I	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							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+															+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 4 5	0 4 4	0 4 5	1 0 5	1 1 2	1 2 1	0 1 4	0 2 3	0 2 4	0 4 2	0 5 2	0 5 3	0 9 1	1 0 2	1 2 4	1 1 3	1 1 5	0 6 3	0 8 2	0 8 5	0 9 2	1 1 3	1 1 4	1 2 2	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	34
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Pars intermedia, adenoma									X																	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, carcinoma								X																		1
General Body System																										
None																										
Genital System																										
Coagulating gland																										3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis			+																				+			4
Preputial gland							+					+											+			12
Prostate	+	+	+	M	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle																					+	+				9
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	M	M	+	+	+	M	M	+	M	M	+	M	+	+	+	+	+	+	M	+	M	+	M	26
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	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma					X																					2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	0 6 2	0 8 5	0 9 6	0 9 9	1 0 5	1 1 2	1 2 9	1 9 7	4 5 7	5 9 5	6 3 7	6 9 5	6 9 9	7 0 1	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	0 6 1	1 0 1	0 3 1	0 2 1	0 6 2	1 1 1	0 8 1	0 4 1	0 6 4	0 2 5	0 7 2	1 0 3	0 8 3	1 1 5	0 3 2	0 3 5	0 4 4	0 6 5	0 7 3	0 7 5	0 8 4	0 9 4	1 2 3	1 1 2	0 1 4
Respiratory System																									
Larynx		+		+		+	+					+													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X				X				X		
Alveolar/bronchiolar carcinoma																X								X	
Hepatocellular carcinoma, metastatic, liver													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland															+										
Adenoma, multiple															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	+	+	M	A	+	A	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed												X		X	X							X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 4 5	0 4 4	0 9 5	1 0 5	1 1 2	1 2 1	0 1 4	0 2 3	0 2 4	0 4 2	0 5 2	0 5 3	0 9 1	1 0 2	1 2 4	0 2 3	0 1 5	0 6 3	0 8 2	0 8 5	0 9 2	1 1 3	1 1 4	1 2 2	**Total Tissues/ Tumors**
Respiratory System																										
Larynx																										5
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X		X							X											6
Alveolar/bronchiolar carcinoma	X			X																						4
Hepatocellular carcinoma, metastatic, liver																								X		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear									+																	1
Harderian gland																										1
Adenoma, multiple																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																		X								1
Lymphoma malignant mixed			X																	X		X				7

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg

Number of Days on Study	0 1 2	0 1 2	0 4 9	0 8 8	1 8 7	1 8 7	2 3 0	3 2 5	4 5 6	5 0 9	5 4 7	6 7 3	6 8 6	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 3 0	7 3 0
Carcass ID Number	3 0 1	3 0 2	3 2 1	2 7 1	3 4 1	3 5 1	3 5 4	3 2 2	3 4 2	3 6 4	2 8 3	3 5 5	3 2 4	2 7 5	2 5 4	2 8 1	2 8 5	2 2 3	2 3 5	3 3 3	3 4 5	3 5 3	3 6 2	2 5 3	2 6 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Gallbladder	A	A	M	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X											
Intestine small	A	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	M	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma										X															
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma, multiple																									
Pancreas	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Pharynx																+	+								
Salivary glands	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth									+							+									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	M	+	+	M	+	+	+	M	+	+	+	M	+	+	M	M	+	I	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thyroid gland	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 6 5	2 7 3	2 8 2	2 8 4	2 9 3	3 3 5	3 5 2	2 5 5	2 6 2	2 6 3	2 9 4	3 1 2	3 1 3	3 1 4	3 3 4	3 6 5	2 5 1	2 5 2	2 7 4	3 0 4	3 0 5	3 1 1	3 3 1	3 3 2	3 4 4	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	38
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Adenocarcinoma																									1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																									1
Hepatocellular carcinoma													X				X								2
Hepatocellular carcinoma, multiple																						X			1
Hepatocellular adenoma, multiple																					X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Pharynx																									2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Squamous cell carcinoma																									1
Stomach, glandular	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Tooth																									2
Cardiovascular System																									
Blood vessel																									14
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	M	+	+	+	+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Follicular cell, adenoma					X																				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0 1 2	0 1 2	0 4 9	0 8 8	1 8 7	1 8 7	2 3 0	3 2 5	4 5 6	5 0 9	5 4 7	6 7 3	6 8 6	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 3 0	7 3 0
Carcass ID Number	3 0 1	3 0 2	3 2 1	2 7 1	3 4 1	3 5 1	3 5 4	3 2 2	3 4 2	3 6 4	2 8 3	3 5 5	3 2 4	2 7 5	2 5 4	2 8 1	2 8 5	2 2 3	3 3 5	3 4 3	3 5 3	3 6 2	2 5 3	2 6 1
General Body System																								
Tissue NOS																								
Genital System																								
Coagulating gland																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis				+						+														
Preputial gland				+		+				+	+					+		+			+	+		+
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle															+									+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	A	+	+	+	+	+	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Fibrosarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+			
Fibrosarcoma																								
Nervous System																								
Brain	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 6 5	2 7 3	2 8 2	2 8 4	2 9 3	3 3 5	3 5 2	2 5 5	2 6 2	2 6 3	2 9 4	3 1 2	3 1 3	3 1 4	3 3 4	3 6 5	2 5 1	2 5 2	2 7 4	3 0 4	3 0 5	3 1 1	3 3 1	3 3 2	3 4 4	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS			+																							1
Genital System																										
Coagulating gland										+																1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+	+					+	+				+					+		+				+			17
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle			+																							3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	M	M	+	+	+	+	+	M	+	M	+	+	M	+	M	+	+	M	+	M	+	+	M	34
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma													X													1
Fibrosarcoma			X				X									X										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle			+																							2
Fibrosarcoma			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0 1 2	0 1 2	0 4 9	0 8 8	1 8 7	1 8 7	2 3 0	3 2 5	4 5 6	5 0 9	5 4 7	6 7 3	6 8 6	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	3 0 1	3 0 2	3 2 1	2 7 1	3 4 1	3 5 1	3 5 4	3 2 2	3 4 2	3 6 4	2 8 3	3 5 5	3 2 4	2 7 5	2 5 4	2 8 1	2 8 5	2 2 3	3 3 5	3 3 3	3 4 5	3 5 3	3 6 2	2 5 3	2 6 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar adenoma, multiple																		X		X					
Carcinoma, metastatic, uncertain primary site																X									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+															
Adenoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	+	+	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 Mercuric Chloride: 5 mg/kg (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	0	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	
	2	2	2	2	2	3	3	2	2	2	2	3	3	3	3	3	2	2	2	3	3	3	3	3	3	**Total**
Carcass ID Number	6	7	8	8	9	3	5	5	6	6	9	1	1	1	3	6	5	5	7	0	0	1	3	3	4	**Tissues/**
	5	3	2	4	3	5	2	5	2	3	4	2	3	4	4	5	1	2	4	4	5	1	1	2	4	**Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X								X								X		X				5
Alveolar/bronchiolar adenoma, multiple									X																	3
Carcinoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+																				+			3
Adenoma			X																				X			3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg

Number of Days on Study	0 0 0 0 1 1 1 1 3 4 4 5 5 5 5 6 6 7 7 7 7 7 7 7 7 0 0 3 4 2 3 3 7 0 7 7 4 4 5 5 4 8 0 2 2 2 2 2 2 2 6 9 1 8 9 6 8 3 9 1 1 4 8 1 5 2 7 4 8 9 9 9 9 9 9
Carcass ID Number	5 5 5 6 5 5 5 5 5 4 5 5 6 5 5 5 5 4 5 4 5 5 5 5 5 1 5 4 0 1 4 1 4 6 9 3 8 0 0 8 3 9 9 3 9 1 7 7 7 9 1 1 1 1 2 2 3 3 4 5 4 5 5 1 1 5 2 4 2 3 5 1 2 3 1
Alimentary System	
Esophagus	+ + + + + + + + + + + + I + + + + + + + + + + + +
Gallbladder	+ + A + + A + A A + + + + A A + A + + + + + + + +
Intestine large	+ +
Intestine large, cecum	+ + A + + A + M + + + + + A + + + + + + + + + + +
Intestine large, colon	+ + + + + A + + + + + + + + + + + + + + + + + + +
Intestine large, rectum	+ + + + + + + + + + I + + + + + + + + + + + + + +
Intestine small	+ + A + + A + + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ + A + + A + A A + + + + A + + + + + + + + + + +
Intestine small, ileum	+ + A + + A A + + + + + + A + M + + + + + + + + +
Intestine small, jejunum	+ + A + + A A A + + + + + A + + + + + + + + + + +
Liver	+ +
Hepatocellular carcinoma	X X
Hepatocellular adenoma	
Mesentery	+
Pancreas	+ + + + + A + + + + + + + + + + + + + + + + + + +
Hemangioma	
Salivary glands	+ + + + + + + + + + + + + + + + + + M + + + + + +
Stomach	+ +
Stomach, forestomach	+ +
Papilloma squamous	
Stomach, glandular	+ + + + + M + + + + + + + + + + + + + + + + + + +
Tooth	
Cardiovascular System	
Blood vessel	+ + + + + + + + + + + + + + + + + + + +
Vena cava, fibrosarcoma, metastatic, skin	X
Heart	+ +
Endocrine System	
Adrenal gland	+ + + + + A + + + + + + + + + + + + + + + + + + +
Adrenal gland, cortex	+ + + + + A + + + + + + + + + + + + + + + + + + +
Subcapsular, adenoma	X
Adrenal gland, medulla	+ + + + + A + + + + + + + + + + + + + + + + + + +
Islets, pancreatic	+ + + + + A + M + + + + + + + + + + + + + + + + +
Parathyroid gland	M + M M + M + M M + + + + + + + M + + + + + M + +
Pituitary gland	+ + + + + M + + + + + + + + + + + + + + + + + + +
Pars intermedia, adenoma	X
Thyroid gland	+ + + + + + + + + I + + + + + + + + + + + + + + +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 0 3	4 9 2	5 0 3	5 0 4	5 2 4	5 3 3	5 5 4	5 6 5	6 0 2	4 9 1	5 2 3	5 3 1	5 4 5	5 5 2	5 6 3	5 9 5	6 0 4	5 0 5	5 2 1	5 4 4	5 5 5	5 6 1	5 6 2	5 7 5	5 8 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X				X														X		X					6
Hepatocellular adenoma																			X							1
Mesentery																				+						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma										X																1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth															+	+									+	3
Cardiovascular System																										
Blood vessel																										18
Vena cava, fibrosarcoma, metastatic, skin																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcapsular, adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	M	+	M	+	+	+	M	+	M	M	+	+	+	+	M	+	+	M	+	M	+	+	M	M	32
Pituitary gland	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	0 0 0 0 1 1 1 1 3 4 4 5 5 5 5 6 6 7 7 7 7 7 7 7 7 0 0 3 4 2 3 3 7 0 7 7 4 4 5 5 4 8 0 2 2 2 2 2 2 2 6 9 1 8 9 6 8 3 9 1 1 4 8 1 5 2 7 4 8 9 9 9 9 9 9
Carcass ID Number	5 5 5 6 5 5 5 5 5 4 5 5 6 5 5 5 5 4 5 4 5 5 5 5 5 1 5 4 0 1 4 1 4 6 9 3 8 0 0 8 3 9 9 3 9 1 7 7 7 9 1 1 1 1 2 2 3 3 4 5 4 5 5 1 1 5 2 4 2 3 5 1 2 3 1
General Body System	
Tissue NOS	+
Mediastinum, fibrosarcoma, metastatic, skin	X
Genital System	
Epididymis	+ +
Penis	+ +
Preputial gland	+
Prostate	+ + + + M + + + + + + + + + + + + + + + + + I + +
Seminal vesicle	+ +
Testes	+ +
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + I + + A + + + + + + + + + + + + + M + + + + + + M
Lymph node, mesenteric	
Spleen	+ + + + + A +
Thymus	+ + + + + + + + + M M + + + I + + M M I 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
Skin	+ +
Fibrosarcoma, metastatic	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	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 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	6 0 3	4 9 2	5 0 3	5 0 4	5 2 4	5 3 3	5 3 4	5 5 5	6 6 5	6 0 2	4 9 1	5 2 3	5 3 1	5 4 5	5 5 2	5 6 3	5 9 5	6 0 4	5 0 5	5 2 1	5 4 4	5 5 5	5 6 1	5 6 2	5 7 5	5 8 3	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Mediastinum, fibrosarcoma, metastatic, skin																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis							+									+	+									6
Preputial gland	+															+										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	46
Seminal vesicle											+															3
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	43
Lymph node, mesenteric											M															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	+	+	M	+	M	M	M	M	+	M	M	M	M	+	+	M	+	+	+	M	M	+	M	27
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	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	0 0 0 0 1 1 1 1 3 4 4 5 5 5 5 6 6 7 7 7 7 7 7 7 7 0 0 3 4 2 3 3 7 0 7 7 4 4 5 5 4 8 0 2 2 2 2 2 2 2 6 9 1 8 9 6 8 3 9 1 1 4 8 1 5 2 7 4 8 9 9 9 9 9 9
Carcass ID Number	5 5 5 6 5 5 5 5 5 4 5 5 6 5 5 5 5 4 5 4 5 5 5 5 5 1 5 4 0 1 4 1 4 6 9 3 8 0 0 8 3 9 9 3 9 1 7 7 7 9 1 1 1 1 2 2 3 3 4 5 4 5 5 1 1 5 2 4 2 3 5 1 2 3 1
Respiratory System	
Larynx	+ + + + + + +
Lung	+ +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar adenoma, multiple	
Alveolar/bronchiolar carcinoma	
Fibrosarcoma, metastatic, skin	X
Hepatocellular carcinoma, metastatic, liver	
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+
Harderian gland	
Adenoma	
Urinary System	
Kidney	+ + + + + A + + + + + + + + + + + + + + + + + + +
Renal tubule, adenocarcinoma	X
Renal tubule, adenoma	X
Ureter	+
Urethra	+ +
Urinary bladder	+ + + + + A + + + + + + M A + + + + + + + I + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant mixed	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	9	0	0	0	0	0	0	0	0	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	
Carcass ID Number	6	4	5	5	5	5	5	5	6	4	5	5	5	5	5	5	6	5	5	5	5	5	5	5	5	**Total**
	0	9	0	0	2	3	5	6	0	9	2	3	4	5	6	9	0	0	2	4	5	6	6	7	8	**Tissues/**
	3	2	3	4	4	3	4	5	2	1	3	1	5	2	3	5	4	5	1	4	5	1	2	5	3	**Tumors**
Respiratory System																										
Larynx																										7
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X							X															3
Alveolar/bronchiolar adenoma, multiple																					X					1
Alveolar/bronchiolar carcinoma										X					X											2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland										+																1
Adenoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenocarcinoma																										1
Renal tubule, adenoma																					X					2
Ureter																										1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed							X									X				X						3

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	5 mg/kg	10 mg/kg
Harderian Gland: Adenoma			
Overall rates[a]	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates[b]	2.8%	7.9%	3.2%
Terminal rates[c]	1/36 (3%)	2/36 (6%)	1/31 (3%)
First incidence (days)	729 (T)	509	729 (T)
Life table tests[d]	P=0.564	P=0.307	P=0.728
Logistic regression tests[d]	P=0.592	P=0.304	P=0.728
Cochran-Armitage test[d]	P=0.610		
Fisher exact test[d]		P=0.309	P=0.753N
Kidney (Renal Tubule): Adenoma or Adenocarcinoma			
Overall rates	0/50 (0%)	0/50 (0%)	3/49 (6%)
Adjusted rates	0.0%	0.0%	9.1%
Terminal rates	0/36 (0%)	0/36 (0%)	2/31 (6%)
First incidence (days)	–[e]	–	642
Life table tests	P=0.029	–[f]	P=0.100
Logistic regression tests	P=0.032	–	P=0.107
Cochran-Armitage test	P=0.036		
Fisher exact test		–	P=0.117
Liver: Hepatocellular Carcinoma			
Overall rates	5/50 (10%)	3/50 (6%)	6/50 (12%)
Adjusted rates	13.5%	8.3%	19.4%
Terminal rates	4/36 (11%)	3/36 (8%)	6/31 (19%)
First incidence (days)	699	729 (T)	729 (T)
Life table tests	P=0.339	P=0.360N	P=0.396
Logistic regression tests	P=0.351	P=0.364N	P=0.409
Cochran-Armitage test	P=0.432		
Fisher exact test		P=0.357N	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	7/50 (14%)	4/50 (8%)	6/50 (12%)
Adjusted rates	18.9%	11.1%	19.4%
Terminal rates	6/36 (17%)	4/36 (11%)	6/31 (19%)
First incidence (days)	699	729 (T)	729 (T)
Life table tests	P=0.542N	P=0.264N	P=0.615N
Logistic regression tests	P=0.528N	P=0.268N	P=0.601N
Cochran-Armitage test	P=0.437N		
Fisher exact test		P=0.262N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	6/50 (12%)	8/50 (16%)	4/50 (8%)
Adjusted rates	16.7%	22.2%	12.9%
Terminal rates	6/36 (17%)	8/36 (22%)	4/31 (13%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.420N	P=0.384	P=0.466N
Logistic regression tests	P=0.420N	P=0.384	P=0.466N
Cochran-Armitage test	P=0.322N		
Fisher exact test		P=0.387	P=0.370N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rates	11.1%	0.0%	6.5%
Terminal rates	4/36 (11%)	0/36 (0%)	2/31 (6%)
First incidence (days)	729 (T)	–	729 (T)
Life table tests	P=0.265N	P=0.063N	P=0.407N
Logistic regression tests	P=0.265N	P=0.063N	P=0.407N
Cochran-Armitage test	P=0.222N		
Fisher exact test		P=0.059N	P=0.339N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	10/50 (20%)	8/50 (16%)	6/50 (12%)
Adjusted rates	27.8%	22.2%	19.4%
Terminal rates	10/36 (28%)	8/36 (22%)	6/31 (19%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.251N	P=0.393N	P=0.303N
Logistic regression tests	P=0.251N	P=0.393N	P=0.303N
Cochran-Armitage test	P=0.170N		
Fisher exact test		P=0.398N	P=0.207N
Skin: Fibrosarcoma			
Overall rates	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rates	5.6%	8.3%	0.0%
Terminal rates	2/36 (6%)	3/36 (8%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	–
Life table tests	P=0.238N	P=0.500	P=0.272N
Logistic regression tests	P=0.238N	P=0.500	P=0.272N
Cochran-Armitage test	P=0.202N		
Fisher exact test		P=0.500	P=0.247N
All Organs: Malignant Lymphoma (Histiocytic or Mixed)			
Overall rates	8/50 (16%)	2/50 (4%)	3/50 (6%)
Adjusted rates	21.0%	4.9%	9.7%
Terminal rates	6/36 (17%)	0/36 (0%)	3/31 (10%)
First incidence (days)	695	456	729 (T)
Life table tests	P=0.083N	P=0.055N	P=0.155N
Logistic regression tests	P=0.065N	P=0.048N	P=0.136N
Cochran-Armitage test	P=0.055N		
Fisher exact test		P=0.046N	P=0.100N
All Organs: Benign Neoplasms			
Overall rates	13/50 (26%)	15/50 (30%)	10/50 (20%)
Adjusted rates	33.9%	40.4%	31.1%
Terminal rates	11/36 (31%)	14/36 (39%)	9/31 (29%)
First incidence (days)	457	509	642
Life table tests	P=0.430N	P=0.406	P=0.466N
Logistic regression tests	P=0.364N	P=0.398	P=0.399N
Cochran-Armitage test	P=0.283N		
Fisher exact test		P=0.412	P=0.318N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
All Organs: Malignant Neoplasms			
Overall rates	20/50 (40%)	11/50 (22%)	12/50 (24%)
Adjusted rates	51.3%	28.1%	37.5%
Terminal rates	17/36 (47%)	8/36 (22%)	11/31 (35%)
First incidence (days)	695	456	728
Life table tests	P=0.110N	P=0.049N	P=0.152N
Logistic regression tests	P=0.075N	P=0.038N	P=0.122N
Cochran-Armitage test	P=0.049N		
Fisher exact test		P=0.041N	P=0.066N
All Organs: Benign or Malignant Neoplasms			
Overall rates	28/50 (56%)	21/50 (42%)	18/50 (36%)
Adjusted rates	70.0%	52.4%	54.5%
Terminal rates	24/36 (67%)	17/36 (47%)	16/31 (52%)
First incidence (days)	457	456	642
Life table tests	P=0.093N	P=0.124N	P=0.114N
Logistic regression tests	P=0.043N	P=0.101N	P=0.062N
Cochran-Armitage test	P=0.028N		
Fisher exact test		P=0.115N	P=0.035N

(T)Terminal sacrifice
[a] Number of neoplasm-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 neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the "Vehicle Control" column 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 neoplasms 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 neoplasms in animal group
[f] Value of statistic cannot be computed

TABLE C4
Historical Incidence of Renal Tubule Neoplasms in Male B6C3F$_1$ Mice Receiving Water by Gavage[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at International Research and Development Corporation			
Resorcinol	0/50	0/50	0/50
Overall Historical Incidence			
Total	0/205 (0.0%)	0/205 (0.0%)	0/205 (0.0%)

[a] Data as of 17 September 1990

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Moribund	6	4	11
Natural deaths	8	10	8
Survivors			
Died last week of study	1		
Terminal sacrifice	35	36	31
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(49)	(48)	(49)
Ulcer, chronic			1 (2%)
Periesophageal tissue, foreign body		1 (2%)	
Periesophageal tissue, inflammation, acute		1 (2%)	
Intestine large, rectum	(47)	(47)	(49)
Prolapse			1 (2%)
Serosa, inflammation, acute		1 (2%)	1 (2%)
Intestine small, jejunum	(48)	(43)	(45)
Peyer's patch, hyperplasia, lymphoid	2 (4%)		
Liver	(50)	(50)	(50)
Abscess, chronic		1 (2%)	
Basophilic focus	2 (4%)		
Clear cell focus			1 (2%)
Congestion	4 (8%)		
Cyst	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus			1 (2%)
Hematopoietic cell proliferation granulocytic		1 (2%)	
Infarct	1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic	3 (6%)		3 (6%)
Inflammation, chronic active		1 (2%)	
Leukocytosis	2 (4%)		
Necrosis		3 (6%)	1 (2%)
Vein, inflammation, chronic active			1 (2%)
Mesentery	(3)		(2)
Inflammation, acute	1 (33%)		1 (50%)
Artery, inflammation, chronic active	1 (33%)		
Fat, necrosis	1 (33%)		
Pancreas	(50)	(46)	(49)
Atrophy	1 (2%)	6 (13%)	3 (6%)
Basophilic focus	1 (2%)		
Inflammation, chronic		1 (2%)	
Inflammation, chronic active		1 (2%)	
Artery, inflammation, chronic active	2 (4%)		
Duct, cyst		2 (4%)	2 (4%)
Pharynx		(2)	
Cyst		1 (50%)	
Inflammation, acute		2 (100%)	

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

	Vehicle Control	5 mg/kg	10 mg/kg
Alimentary System (continued)			
Salivary glands	(50)	(48)	(49)
Atrophy		1 (2%)	1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Stomach, forestomach	(50)	(48)	(50)
Hyperplasia, squamous			3 (6%)
Stomach, glandular	(49)	(47)	(49)
Erosion	1 (2%)		
Infiltration cellular, mast cell	1 (2%)		
Inflammation, chronic		1 (2%)	
Tooth	(3)	(2)	(3)
Developmental malformation	2 (67%)	1 (50%)	
Periodontal tissue, inflammation, acute	1 (33%)		1 (33%)
Periodontal tissue, inflammation, chronic active	1 (33%)		
Periodontal tissue, inflammation, granulomatous			2 (67%)
Cardiovascular System			
Heart	(50)	(50)	(50)
Abscess			1 (2%)
Degeneration	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)
Mineralization	7 (14%)	1 (2%)	
Thrombus	1 (2%)		
Coronary artery, inflammation, chronic active		1 (2%)	
Epicardium, fibrosis			1 (2%)
Epicardium, inflammation, acute		1 (2%)	
Valve, thrombus	1 (2%)		
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(49)
Congestion		1 (2%)	
Cyst	1 (2%)		
Hyperplasia	2 (4%)		
Hypertrophy, focal	3 (6%)	4 (8%)	1 (2%)
Subcapsular, hyperplasia	41 (82%)	38 (76%)	36 (73%)
Islets, pancreatic	(49)	(47)	(48)
Hyperplasia	3 (6%)	2 (4%)	
Parathyroid gland	(34)	(34)	(32)
Cyst	2 (6%)		
Pituitary gland	(48)	(47)	(47)
Cyst		1 (2%)	1 (2%)
Hyperplasia			1 (2%)
Thyroid gland	(49)	(47)	(49)
Inflammation, chronic		1 (2%)	1 (2%)
Follicle, crystals			1 (2%)
Follicle, cyst	1 (2%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia			1 (2%)

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

	Vehicle Control	5 mg/kg	10 mg/kg
General Body System			
Tissue NOS		(1)	(1)
Fat, pelvic, inflammation, chronic		1 (100%)	
Mediastinum, angiectasis		1 (100%)	
Genital System			
Epididymis	(50)	(50)	(50)
Dilatation			2 (4%)
Granuloma sperm			1 (2%)
Hypospermia	1 (2%)		
Inflammation, chronic			1 (2%)
Penis	(4)	(2)	(6)
Inflammation, acute	2 (50%)		
Inflammation, chronic active		1 (50%)	
Preputial gland	(12)	(17)	(3)
Abscess	3 (25%)	4 (24%)	1 (33%)
Inflammation, acute	2 (17%)		
Inflammation, chronic	1 (8%)	3 (18%)	1 (33%)
Inflammation, chronic active	3 (25%)		1 (33%)
Duct, cyst	7 (58%)	14 (82%)	3 (100%)
Prostate	(46)	(49)	(46)
Inflammation, acute	2 (4%)	4 (8%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	1 (2%)		2 (4%)
Seminal vesicle	(9)	(3)	(3)
Dilatation	2 (22%)	1 (33%)	
Testes	(50)	(50)	(50)
Degeneration	4 (8%)	2 (4%)	7 (14%)
Artery, inflammation, chronic	1 (2%)		
Seminiferous tubule, dilatation, focal			1 (2%)
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Infiltration cellular, mast cell	1 (2%)		
Myeloid cell, hyperplasia	4 (8%)	2 (4%)	4 (8%)
Lymph node	(44)	(48)	(43)
Axillary, hyperplasia, plasma cell		1 (2%)	
Iliac, hyperplasia, lymphoid	1 (2%)		
Iliac, hyperplasia, plasma cell		2 (4%)	
Inguinal, hyperplasia, lymphoid	2 (5%)		2 (5%)
Inguinal, hyperplasia, plasma cell	1 (2%)	2 (4%)	
Inguinal, pigmentation	1 (2%)		3 (7%)
Mandibular, infiltration cellular, histiocyte			1 (2%)
Mediastinal, hyperplasia, lymphoid	2 (5%)		2 (5%)
Mediastinal, inflammation, acute	1 (2%)		
Mesenteric, hyperplasia, lymphoid		2 (4%)	2 (5%)
Pancreatic, hematopoietic cell proliferation	1 (2%)		

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

	Vehicle Control	5 mg/kg	10 mg/kg
Hematopoietic System (continued)			
Spleen	(50)	(49)	(49)
Hematopoietic cell proliferation	3 (6%)	1 (2%)	4 (8%)
Hematopoietic cell proliferation granulocytic	1 (2%)	1 (2%)	
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		3 (6%)
Thymus	(26)	(34)	(27)
Atrophy	1 (4%)		3 (11%)
Cyst	4 (15%)	6 (18%)	2 (7%)
Ectopic parathyroid gland	1 (4%)		
Hyperplasia, lymphoid		1 (3%)	
Necrosis	5 (19%)	1 (3%)	5 (19%)
Epithelial cell, hyperplasia			2 (7%)
Integumentary System			
Skin	(50)	(50)	(50)
Abscess			1 (2%)
Acanthosis		3 (6%)	
Fibrosis		1 (2%)	
Hyperplasia, squamous, focal		1 (2%)	
Inflammation, acute	3 (6%)		2 (4%)
Inflammation, chronic	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)		
Ulcer		1 (2%)	1 (2%)
Abdominal, abscess			1 (2%)
Face, cyst		1 (2%)	
Inguinal, ulcer		1 (2%)	
Prepuce, abscess	1 (2%)		
Prepuce, ulcer	1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, inflammation, granulomatous			1 (2%)
Musculoskeletal System			
Skeletal muscle	(2)	(2)	
Abdominal, inflammation, acute	1 (50%)		
Abdominal, mineralization	1 (50%)		
Thoracic, inflammation, acute	1 (50%)		
Thoracic, metaplasia		1 (50%)	
Nervous System			
Brain	(50)	(49)	(50)
Congestion	1 (2%)		
Hemorrhage	1 (2%)		
Mineralization	21 (42%)	29 (59%)	26 (52%)

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

	Vehicle Control	5 mg/kg	10 mg/kg
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	3 (6%)	3 (6%)	2 (4%)
Hemorrhage		4 (8%)	1 (2%)
Inflammation, acute	1 (2%)		3 (6%)
Leukocytosis	2 (4%)		1 (2%)
Mineralization		1 (2%)	
Thrombus		1 (2%)	
Alveolar epithelium, hyperplasia, focal	3 (6%)	1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	2 (4%)		3 (6%)
Artery, thrombus	1 (2%)		
Perivascular, infiltration cellular, lymphocyte			1 (2%)
Pleura, fibrosis			1 (2%)
Pleura, inflammation, acute		1 (2%)	
Vein, thrombus			3 (6%)
Nose	(50)	(50)	(50)
Angiectasis		1 (2%)	
Exudate	3 (6%)	9 (18%)	20 (40%)
Inflammation, acute	1 (2%)	3 (6%)	14 (28%)
Inflammation, chronic			1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)
Nasolacrimal duct, cyst			1 (2%)
Olfactory epithelium, metaplasia	3 (6%)	8 (16%)	41 (82%)
Trachea	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Peritracheal tissue, foreign body		1 (2%)	
Peritracheal tissue, inflammation, acute		1 (2%)	
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(49)
Autolysis		1 (2%)	
Cyst	4 (8%)	2 (4%)	9 (18%)
Hydronephrosis	1 (2%)		1 (2%)
Infarct	1 (2%)		
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)
Nephropathy	40 (80%)	45 (90%)	44 (90%)
Artery, inflammation, chronic active	2 (4%)		
Glomerulus, inflammation, acute	1 (2%)		
Pelvis, inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Pelvis, transitional epithelium, hyperplasia			1 (2%)
Renal tubule, hyperplasia			2 (4%)
Renal tubule, hyperplasia, focal	1 (2%)		
Ureter			(1)
Inflammation, chronic			1 (100%)

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

	Vehicle Control	5 mg/kg	10 mg/kg
Urinary System (continued)			
Urethra	(1)	(1)	(2)
Dilatation	1 (100%)		1 (50%)
Inflammation, acute		1 (100%)	
Inflammation, chronic active			1 (50%)
Urinary bladder	(45)	(48)	(46)
Calculus gross observation	1 (2%)	2 (4%)	
Calculus micro observation only	2 (4%)		1 (2%)
Dilatation	1 (2%)		
Inflammation, acute	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic active	1 (2%)		2 (4%)
Mineralization			1 (2%)
Transitional epithelium, hyperplasia			1 (2%)

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

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF MERCURIC CHLORIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Accidental deaths			1
Moribund	4	11	8
Natural deaths	5	4	10
Survivors			
Terminal sacrifice	41	35	31
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Gallbladder	(38)	(41)	(35)
Intestine large, cecum	(45)	(49)	(42)
Intestine large, colon	(49)	(50)	(48)
Intestine large, rectum	(44)	(46)	(49)
Intestine small, duodenum	(45)	(47)	(43)
Intestine small, jejunum	(48)	(48)	(41)
Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
Hemangiosarcoma, metastatic, spleen			1 (2%)
Hepatocellular carcinoma	2 (4%)		
Hepatocellular carcinoma, multiple		1 (2%)	
Hepatocellular adenoma	1 (2%)		2 (4%)
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Mesentery	(6)	(1)	(3)
Pancreas	(50)	(50)	(47)
Salivary glands	(49)	(48)	(50)
Stomach, forestomach	(48)	(50)	(48)
Papilloma squamous			2 (4%)
Squamous cell carcinoma	1 (2%)		1 (2%)
Stomach, glandular	(48)	(50)	(47)
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Cardiovascular System			
Blood vessel	(6)	(8)	(17)
Heart	(50)	(50)	(50)
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(50)
Adenoma			1 (2%)
Adrenal gland, medulla	(49)	(48)	(49)
Pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(49)	(50)	(46)
Adenoma		1 (2%)	

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

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System (continued)			
Pituitary gland	(49)	(47)	(45)
Adenoma	2 (4%)	4 (9%)	2 (4%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	(49)	(49)
Follicular cell, adenoma		1 (2%)	
General Body System			
Tissue NOS	(1)	(3)	(3)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (33%)	1 (33%)
Mediastinum, hemangiosarcoma		1 (33%)	
Genital System			
Ovary	(49)	(49)	(50)
Adenoma	4 (8%)	1 (2%)	1 (2%)
Granulosa cell neoplasm benign	1 (2%)		
Teratoma			1 (2%)
Oviduct			(1)
Uterus	(50)	(50)	(49)
Hemangioma		1 (2%)	
Hemangiosarcoma		1 (2%)	1 (2%)
Leiomyosarcoma		1 (2%)	
Cervix, granular cell neoplasm benign			1 (2%)
Cervix, endometrium, polyp stromal			1 (2%)
Endometrium, polyp stromal	2 (4%)		
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Lymph node	(44)	(44)	(48)
Mesenteric, squamous cell carcinoma, metastatic, stomach			1 (2%)
Spleen	(49)	(50)	(48)
Hemangioma			1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)
Thymus	(41)	(39)	(43)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (3%)	1 (2%)
Integumentary System			
Mammary gland	(47)	(46)	(46)
Adenocarcinoma			1 (2%)
Skin	(50)	(50)	(50)
Fibrosarcoma		4 (8%)	
Hemangiosarcoma		1 (2%)	

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

	Vehicle Control	5 mg/kg	10 mg/kg
Musculoskeletal System			
Bone	(50)	(50)	(50)
Skeletal muscle	(3)		(1)
Nervous System			
Brain	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Respiratory System			
Lung	(50)	(50)	(50)
Adenocarcinoma, metastatic, harderian gland			1 (2%)
Alveolar/bronchiolar adenoma	2 (4%)	5 (10%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	
Squamous cell carcinoma, metastatic, stomach			1 (2%)
Nose	(50)	(50)	(50)
Trachea	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Special Senses System			
Harderian gland		(1)	(1)
Adenocarcinoma			1 (100%)
Adenoma		1 (100%)	
Urinary System			
Kidney	(49)	(50)	(50)
Urinary bladder	(48)	(48)	(47)
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	9 (18%)	8 (16%)	4 (8%)

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

	Vehicle Control	5 mg/kg	10 mg/kg
Neoplasm Summary			
Total animals with primary neoplasms[c]	23	32	19
Total primary neoplasms	29	39	28
Total animals with benign neoplasms	13	14	12
Total benign neoplasms	14	15	16
Total animals with malignant neoplasms	14	21	12
Total malignant neoplasms	15	24	12
Total animals with metastatic neoplasms		2	4
Total metastatic neoplasms		4	8

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control

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

+: 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 Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 4	2 0 2	2 0 4	2 1 5	2 2 5	1 3 2	1 5 1	1 5 4	1 6 3	1 8 3	1 9 2	1 9 3	2 1 1	2 2 4	2 4 2	1 3 4	1 4 1	1 4 4	1 7 1	1 7 3	1 8 2	2 3 1	2 3 4	2 3 5	2 4 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										1
Hepatocellular carcinoma							X																			2
Hepatocellular adenoma																		X								1
Mesentery																							+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel																										6
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			2
Pars intermedia, adenoma																	X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	2 1 3 5	5 3 6 0	5 6 6 5	5 9 5 3	6 7 7 1	7 0 0 5	7 0 1 7	7 1 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 2 9	7 2 3 0	7 3 3 0	7 3 3 0	7 3 3 0	7 3 3 0
Carcass ID Number	2 4 1 1	1 9 5 1	2 2 1 2	2 2 2 5	1 7 5 2	1 4 2 1	1 8 1 3	2 3 1 4	2 1 3 5	1 3 5 2	1 5 6 2	1 6 6 2	1 6 7 5	1 7 0 4	2 0 0 1	2 0 1 5	2 1 1 2	2 1 3 3	2 3 2 2	2 4 3 5	1 3 5 3	1 5 6 1	1 6 6 4	1 8 8 4
General Body System																								
Tissue NOS							+																	
Genital System																								
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Granulosa cell tumor benign																	X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal																			X					
Vagina							+	+																
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Thymus	+	+	+	M	+	+	M	M	M	M	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+					+			+												
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx																		+						
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 4	2 0 2	2 0 4	2 1 5	2 2 5	1 3 2	1 5 1	1 5 4	1 6 3	1 8 3	1 9 2	1 9 3	1 2 1	2 2 4	2 4 2	1 3 4	1 4 1	1 4 4	1 7 1	1 7 3	1 8 2	2 3 1	2 3 4	2 3 5	2 4 3	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X													X							X					4
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal					X																					2
Vagina												+									+					4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	41
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X														X											2
Alveolar/bronchiolar carcinoma																									X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: Vehicle Control (continued)

Number of Days on Study	2 1 1	5 3 5	5 6 0	5 6 5	5 9 3	6 7 1	7 0 0	7 0 5	7 1 7	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	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 4 1	1 9 5	2 2 1	2 2 2	1 7 5	1 4 2	1 8 1	2 3 3	2 1 4	1 3 5	1 5 2	1 6 2	1 6 5	1 7 4	2 0 1	2 0 5	2 1 2	2 1 3	2 3 2	2 4 5	1 3 3	1 5 3	1 6 1	1 6 4	1 8 4
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed			X			X		X	X														X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 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 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 9 4	2 0 2	2 0 4	2 1 5	2 2 5	1 3 2	1 5 1	1 5 4	1 6 3	1 8 3	1 9 2	1 9 3	2 1 1	2 2 4	2 4 2	1 3 4	1 4 1	1 4 4	1 7 1	1 7 3	1 8 2	2 3 1	2 3 4	2 3 5	2 4 3	**Total Tissues/ Tumors**
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X									X											X			X		9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	3 9 4	3 9 5	4 2 2	4 3 1	4 3 2	4 4 1	4 5 3	4 8 5	3 7 1	3 8 2	3 8 5	4 2 3	4 4 3	4 6 3	4 7 4	4 8 2	4 8 3	3 8 3	3 9 1	4 1 4	4 1 5	4 2 5	4 4 2	4 5 4	4 6 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	M	+	+	M	+	+	M	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma, multiple						X																				1
Mesentery																	+									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth														+												1
Cardiovascular System																										
Blood vessel																										8
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	39
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X			X																			X			4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0	4	4	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	6	5	3	3	7	7	7	8	0	0	0	1	1	2	2	2	2	2	2	2	2	3
	7	0	4	8	2	9	0	3	8	0	1	4	9	5	9	9	9	9	9	9	9	9	9	0
Carcass ID Number	4	3	3	3	4	4	4	4	4	4	4	4	4	3	4	3	3	3	4	4	4	4	4	3
	0	7	8	7	4	6	1	7	1	3	6	6	0	8	2	7	7	9	0	0	3	7	8	9
	1	2	1	5	5	2	1	2	2	4	4	5	3	4	4	3	4	3	2	4	5	1	4	2
General Body System																								
Tissue NOS		+							+														+	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		X																						
Mediastinum, hemangiosarcoma									X															
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Hemangiosarcoma																							X	
Leiomyosarcoma																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X					X										
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	M	M
Alveolar/bronchiolar carcinoma, metastatic, lung																						X		
Integumentary System																								
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X				X												
Hemangiosarcoma														X										
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X																						
Spinal cord																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (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 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	3 9 4	3 9 5	4 2 2	4 3 1	4 3 2	4 4 1	4 5 3	4 8 5	3 7 1	3 8 2	3 8 5	4 2 3	4 4 3	4 6 3	4 7 4	4 8 2	4 8 3	4 8 3	3 9 1	3 1 4	4 1 5	4 1 5	4 2 5	4 4 2	4 5 4	4 6 1	**Total Tissues/ Tumors**
General Body System																											
Tissue NOS																											3
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Mediastinum, hemangiosarcoma																											1
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		49
Adenoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangioma												X															1
Hemangiosarcoma																											1
Leiomyosarcoma											X																1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	M	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	I	+		44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											2
Thymus	M	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	M	+	M	M	+	+		39
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		46
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Fibrosarcoma																				X				X			4
Hemangiosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Spinal cord																			+								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 5 mg/kg (continued)

Number of Days on Study	0	4	4	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	0	6	5	3	3	7	7	7	8	0	0	0	1	1	2	2	2	2	2	2	2	2	2	3
	7	0	4	8	2	9	0	3	8	0	1	4	9	5	9	9	9	9	9	9	9	9	9	9	0
Carcass ID Number	4	3	3	3	4	4	4	4	4	4	4	4	4	3	4	3	3	3	4	4	4	4	4	4	3
	0	7	8	7	4	6	1	7	1	3	6	6	0	8	2	7	7	9	0	0	3	7	7	8	9
	1	2	1	5	5	2	1	2	2	4	4	5	3	4	4	3	4	3	2	4	5	1	3	4	2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X		X	X								X						
Alveolar/bronchiolar carcinoma																						X			
Alveolar/bronchiolar carcinoma, multiple		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung		X																							
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter	+																								
Urethra		+																							
Urinary bladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
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 Mercuric Chloride: 5 mg/kg (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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	3 9 4	3 9 5	4 2 2	4 3 1	4 3 2	4 4 1	4 5 3	4 8 5	3 7 1	3 8 2	3 8 5	4 2 3	4 4 3	4 6 3	4 7 4	4 8 2	4 8 3	3 8 3	3 9 1	4 1 4	4 1 5	4 2 5	4 4 2	4 5 4	4 6 1	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	5
Alveolar/bronchiolar carcinoma																			X							2
Alveolar/bronchiolar carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Special Senses System																										
Harderian gland								+																		1
Adenoma								X																		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																					X					1
Lymphoma malignant mixed																	X	X								8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg

Number of Days on Study	0 8 2	3 2 5	3 2 5	3 6 4	4 3 2	4 7 1	4 9 2	5 5 1	5 6 2	5 7 3	6 3 7	6 5 1	6 5 6	6 6 1	6 6 9	6 7 0	6 7 2	6 8 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	7 1 5	6 6 1	6 7 1	7 2 5	6 7 3	6 7 5	7 2 1	6 2 4	6 4 3	6 6 5	6 1 4	7 1 4	6 7 4	7 0 2	6 5 2	7 2 3	6 4 4	6 3 4	6 6 2	6 2 3	6 2 5	6 4 5	6 9 2	6 9 4	6 9 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	A	A	+	+	A	+	+	+	+	A	A	+	+	+	A	+	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	A	A	A	+	+	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	M	A	+	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	A	+	+	A	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen												X													
Hepatocellular adenoma													X												
Squamous cell carcinoma, metastatic, stomach																		X							
Mesentery																	+					+			
Pancreas	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous												X													
Squamous cell carcinoma																		X							
Stomach, glandular	M	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach																		X							
Tongue																									
Tooth																						+			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	7 1 1	7 2 4	6 1 1	6 1 3	6 1 5	6 3 5	6 5 4	6 8 2	6 8 5	7 0 1	6 1 2	6 4 2	6 5 5	6 9 1	6 9 3	7 0 3	7 0 4	7 2 2	6 2 1	6 5 3	6 6 3	6 6 4	7 0 5	7 1 2	7 1 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	35
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular adenoma														X												2
Squamous cell carcinoma, metastatic, stomach																										1
Mesentery																	+									3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous										X																2
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, stomach																										1
Tongue									+																	1
Tooth																										1
Cardiovascular System																										
Blood vessel																										17
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign													X													1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	0 8 2	3 2 5	3 2 5	3 6 4	4 3 2	4 7 1	4 9 2	5 5 1	5 6 2	5 7 3	6 3 7	6 5 1	6 5 6	6 6 1	6 6 9	6 7 0	6 7 2	6 8 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	7 1 5	6 6 1	6 7 1	7 2 5	6 7 3	6 7 5	7 2 1	6 2 4	6 4 3	6 6 5	6 1 4	7 1 4	6 7 4	7 0 2	6 5 2	7 2 3	6 4 4	6 3 4	6 6 2	6 2 3	6 2 5	6 4 5	6 9 2	6 9 4	6 9 5
Endocrine System (continued)																									
Islets, pancreatic	M	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	M	M	M	+	+	M	M	M	M	M	+	M	M	+	+	+	M	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+
Adenoma							X															X			
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Tissue NOS												+	+				+								
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung													X												
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Teratoma																X									
Oviduct																						+			
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Cervix, granular cell tumor benign																									
Cervix, endometrium, polyp stromal																									
Vagina	+													+		+				+					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenteric, squamous cell carcinoma, metastatic, stomach																		X							
Spleen	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Hemangiosarcoma											X														
Thymus	+	+	+	M	M	M	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	7 1 1	7 2 4	6 1 1	6 1 3	6 1 5	6 3 5	6 5 4	6 8 2	6 8 5	7 0 1	6 1 2	6 4 2	6 5 5	6 9 1	6 9 3	7 0 3	7 0 4	7 2 2	6 2 1	6 5 3	6 6 3	6 6 4	7 0 5	7 1 2	7 1 3	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	M	+	M	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	45
Adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
Tissue NOS																										3
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Teratoma																										1
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Cervix, granular cell tumor benign									X																	1
Cervix, endometrium, polyp stromal						X																				1
Vagina				+													+	+	+							8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Mesenteric, squamous cell carcinoma, metastatic, stomach																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																										1
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	43
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma	X																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	0 8 2	3 2 5	3 2 5	3 6 4	4 3 2	4 7 1	4 9 2	5 5 1	5 6 2	5 7 3	6 3 7	6 5 1	6 5 6	6 6 1	6 6 9	6 7 0	6 7 2	6 8 8	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	7 1 5	6 6 1	6 7 1	7 2 5	6 7 3	6 7 5	7 2 1	6 2 4	6 4 3	6 6 5	6 1 4	7 1 4	6 7 4	7 0 2	6 5 2	7 2 3	6 4 4	6 3 4	6 6 2	6 2 3	6 2 5	6 4 5	6 9 2	6 9 4	6 9 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx				+														+							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma										X			X												
Squamous cell carcinoma, metastatic, stomach																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenocarcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant mixed																X			X			X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Mercuric Chloride: 10 mg/kg (continued)

Number of Days on Study	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 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	7 1 1	7 2 4	6 1 1	6 1 3	6 1 5	6 3 5	6 5 4	6 8 2	6 8 5	7 0 1	6 1 2	6 4 2	6 5 5	6 9 1	6 9 3	7 0 3	7 0 4	7 2 2	6 2 1	6 5 3	6 6 3	6 6 4	7 0 5	7 1 2	7 1 3	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx																										2
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland						X																				1
Alveolar/bronchiolar adenoma						X																			X	2
Alveolar/bronchiolar adenoma, multiple													X													1
Alveolar/bronchiolar carcinoma																										2
Squamous cell carcinoma, metastatic, stomach																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+																				1
Adenocarcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																	X									4

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Mercuric Chloride

	Vehicle Control	5 mg/kg	10 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates[a]	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates[b]	7.3%	2.9%	5.8%
Terminal rates[c]	3/41 (7%)	1/35 (3%)	1/31 (3%)
First incidence (days)	729 (T)	729 (T)	656
Life table tests[d]	P=0.505N	P=0.363N	P=0.615N
Logistic regression tests[d]	P=0.462N	P=0.363N	P=0.569N
Cochran-Armitage test[d]	P=0.399N		
Fisher exact test[d]		P=0.309N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rates	4.9%	12.4%	9.7%
Terminal rates	2/41 (5%)	2/35 (6%)	3/31 (10%)
First incidence (days)	729 (T)	673	729 (T)
Life table tests	P=0.284	P=0.179	P=0.373
Logistic regression tests	P=0.342	P=0.209	P=0.373
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.218	P=0.500
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rates	2.4%	7.6%	5.0%
Terminal rates	1/41 (2%)	2/35 (6%)	0/31 (0%)
First incidence (days)	729 (T)	400	573
Life table tests	P=0.326	P=0.266	P=0.435
Logistic regression tests	P=0.453	P=0.328	P=0.531
Cochran-Armitage test	P=0.399		
Fisher exact test		P=0.309	P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	3/50 (6%)	8/50 (16%)	5/50 (10%)
Adjusted rates	7.3%	19.4%	14.2%
Terminal rates	3/41 (7%)	4/35 (11%)	3/31 (10%)
First incidence (days)	729 (T)	400	573
Life table tests	P=0.185	P=0.075	P=0.235
Logistic regression tests	P=0.304	P=0.104	P=0.310
Cochran-Armitage test	P=0.314		
Fisher exact test		P=0.100	P=0.357
Ovary: Adenoma			
Overall rates	4/49 (8%)	1/49 (2%)	1/50 (2%)
Adjusted rates	9.8%	2.9%	2.9%
Terminal rates	4/41 (10%)	1/34 (3%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	670
Life table tests	P=0.161N	P=0.239N	P=0.272N
Logistic regression tests	P=0.131N	P=0.239N	P=0.225N
Cochran-Armitage test	P=0.098N		
Fisher exact test		P=0.181N	P=0.175N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	2/49 (4%)	4/47 (9%)	2/45 (4%)
Adjusted rates	4.9%	11.8%	5.8%
Terminal rates	2/41 (5%)	4/34 (12%)	1/28 (4%)
First incidence (days)	729 (T)	729 (T)	492
Life table tests	P=0.425	P=0.254	P=0.577
Logistic regression tests	P=0.518	P=0.254	P=0.679
Cochran-Armitage test	P=0.548		
Fisher exact test		P=0.319	P=0.659
Skin: Fibrosarcoma			
Overall rates	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rates	0.0%	10.3%	0.0%
Terminal rates	0/41 (0%)	2/35 (6%)	0/31 (0%)
First incidence (days)	–[e]	673	–
Life table tests	P=0.531	P=0.053	–[f]
Logistic regression tests	P=0.589	P=0.061	–
Cochran-Armitage test	P=0.622		
Fisher exact test		P=0.059	–
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma			
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rates	2.4%	0.0%	8.6%
Terminal rates	1/41 (2%)	0/35 (0%)	1/31 (3%)
First incidence (days)	729 (T)	–	651
Life table tests	P=0.129	P=0.532N	P=0.225
Logistic regression tests	P=0.159	P=0.532N	P=0.275
Cochran-Armitage test	P=0.176		
Fisher exact test		P=0.500N	P=0.309
All Organs: Hemangiosarcoma			
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rates	2.4%	7.7%	5.7%
Terminal rates	1/41 (2%)	1/35 (3%)	1/31 (3%)
First incidence (days)	729 (T)	678	651
Life table tests	P=0.305	P=0.266	P=0.419
Logistic regression tests	P=0.362	P=0.296	P=0.467
Cochran-Armitage test	P=0.399		
Fisher exact test		P=0.309	P=0.500
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rates	2.4%	10.4%	8.3%
Terminal rates	1/41 (2%)	2/35 (6%)	1/31 (3%)
First incidence (days)	729 (T)	678	651
Life table tests	P=0.169	P=0.147	P=0.230
Logistic regression tests	P=0.218	P=0.170	P=0.282
Cochran-Armitage test	P=0.252		
Fisher exact test		P=0.181	P=0.309

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)			
Overall rates	9/50 (18%)	9/50 (18%)	5/50 (10%)
Adjusted rates	19.8%	21.9%	13.8%
Terminal rates	5/41 (12%)	4/35 (11%)	2/31 (6%)
First incidence (days)	560	558	364
Life table tests	P=0.340N	P=0.491	P=0.363N
Logistic regression tests	P=0.170N	P=0.600	P=0.188N
Cochran-Armitage test	P=0.166N		
Fisher exact test		P=0.602N	P=0.194N
All Organs: Benign Neoplasms			
Overall rates	13/50 (26%)	14/50 (28%)	12/50 (24%)
Adjusted rates	31.7%	35.1%	32.2%
Terminal rates	13/41 (32%)	10/35 (29%)	7/31 (23%)
First incidence (days)	729 (T)	632	492
Life table tests	P=0.336	P=0.337	P=0.390
Logistic regression tests	P=0.502	P=0.453	P=0.551
Cochran-Armitage test	P=0.455N		
Fisher exact test		P=0.500	P=0.500N
All Organs: Malignant Neoplasms			
Overall rates	14/50 (28%)	21/50 (42%)	12/50 (24%)
Adjusted rates	31.0%	46.5%	30.7%
Terminal rates	10/41 (24%)	11/35 (31%)	5/31 (16%)
First incidence (days)	560	400	364
Life table tests	P=0.389	P=0.065	P=0.484
Logistic regression tests	P=0.409N	P=0.100	P=0.448N
Cochran-Armitage test	P=0.373N		
Fisher exact test		P=0.104	P=0.410N
All Organs: Benign or Malignant Neoplasms			
Overall rates	23/50 (46%)	32/50 (64%)	19/50 (38%)
Adjusted rates	51.0%	69.5%	46.8%
Terminal rates	19/41 (46%)	21/35 (60%)	10/31 (32%)
First incidence (days)	560	400	364
Life table tests	P=0.375	P=0.023	P=0.478
Logistic regression tests	P=0.341N	P=0.043	P=0.365N
Cochran-Armitage test	P=0.242N		
Fisher exact test		P=0.054	P=0.272N

(T)Terminal sacrifice

[a] Number of neoplasm-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 neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the "Vehicle Control" column 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 neoplasms 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 neoplasms in animal group

[f] Value of statistic cannot be computed

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-month interim evaluation	10	10	10
Early deaths			
Accidental deaths			1
Moribund	4	11	8
Natural deaths	5	4	10
Survivors			
Terminal sacrifice	41	35	31
Animls examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(50)	(50)
Erosion		1 (2%)	
Inflammation, chronic active		1 (2%)	
Gallbladder	(38)	(41)	(35)
Cyst	1 (3%)		1 (3%)
Inflammation, chronic		4 (10%)	
Intestine large	(49)	(50)	(50)
Anus, inflammation, acute			1 (2%)
Intestine large, cecum	(45)	(49)	(42)
Parasite metazoan		1 (2%)	
Serosa, fibrosis	1 (2%)		
Intestine large, colon	(49)	(50)	(48)
Serosa, fibrosis	1 (2%)	1 (2%)	
Intestine large, rectum	(44)	(46)	(49)
Submucosa, cyst		1 (2%)	
Intestine small, duodenum	(45)	(47)	(43)
Serosa, fibrosis		1 (2%)	
Intestine small, ileum	(47)	(44)	(44)
Peyer's patch, hyperplasia, lymphoid	2 (4%)		
Serosa, fibrosis	1 (2%)		
Intestine small, jejunum	(48)	(48)	(41)
Hyperplasia, lymphoid		2 (4%)	
Serosa, fibrosis	1 (2%)		
Liver	(50)	(50)	(50)
Angiectasis		2 (4%)	1 (2%)
Clear cell focus	1 (2%)		1 (2%)
Congestion	2 (4%)		
Eosinophilic focus	1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	13 (26%)	21 (42%)	18 (36%)
Inflammation, chronic active		1 (2%)	
Necrosis		3 (6%)	3 (6%)
Pigmentation		1 (2%)	1 (2%)
Thrombus	1 (2%)		
Hepatocyte, atrophy			1 (2%)
Perivascular, infiltration cellular, lymphocyte		1 (2%)	
Serosa, fibrosis	1 (2%)	1 (2%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Alimentary System (continued)			
Mesentery	(6)	(1)	(3)
Inflammation, chronic	1 (17%)		
Inflammation, chronic active			1 (33%)
Fat, necrosis	3 (50%)		
Pancreas	(50)	(50)	(47)
Atrophy	3 (6%)	3 (6%)	1 (2%)
Eosinophilic focus	1 (2%)		2 (4%)
Fibrosis		2 (4%)	
Hyperplasia, lymphoid		1 (2%)	
Inflammation, chronic	1 (2%)	3 (6%)	
Duct, cyst	5 (10%)	3 (6%)	
Salivary glands	(49)	(48)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic		1 (2%)	
Stomach, forestomach	(48)	(50)	(48)
Hyperkeratosis	1 (2%)		2 (4%)
Hyperplasia, squamous		2 (4%)	3 (6%)
Inflammation, chronic		1 (2%)	
Serosa, fibrosis		1 (2%)	
Stomach, glandular	(48)	(50)	(47)
Erosion	1 (2%)	3 (6%)	2 (4%)
Ulcer, multiple		1 (2%)	
Serosa, fibrosis		1 (2%)	
Tongue			(1)
Hyperplasia, squamous			1 (100%)
Tooth		(1)	(1)
Developmental malformation			1 (100%)
Periodontal tissue, inflammation, granulomatous		1 (100%)	
Cardiovascular System			
Heart	(50)	(50)	(50)
Degeneration			1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
Mineralization	2 (4%)	1 (2%)	
Coronary artery, inflammation, chronic active		1 (2%)	
Epicardium, fibrosis		1 (2%)	
Epicardium, inflammation, chronic active			1 (2%)
Valve, thrombus			1 (2%)
Endocrine System			
Adrenal gland, cortex	(49)	(49)	(50)
Congestion		1 (2%)	
Cyst			1 (2%)
Degeneration	1 (2%)		
Hematopoietic cell proliferation			1 (2%)
Hemorrhage			1 (2%)
Hypertrophy, focal	1 (2%)	1 (2%)	2 (4%)
Mineralization			1 (2%)
Subcapsular, hyperplasia	48 (98%)	48 (98%)	50 (100%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Endocrine System (continued)			
Adrenal gland, medulla	(49)	(48)	(49)
Hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)
Islets, pancreatic	(49)	(50)	(46)
Hyperplasia	1 (2%)		1 (2%)
Pituitary gland	(49)	(47)	(45)
Cyst	1 (2%)		
Hyperplasia, focal	4 (8%)	4 (9%)	3 (7%)
Thyroid gland	(50)	(49)	(49)
Inflammation, acute		1 (2%)	
Inflammation, chronic		2 (4%)	
Follicle, cyst	2 (4%)	3 (6%)	3 (6%)
Follicular cell, hyperplasia	1 (2%)	1 (2%)	3 (6%)
General Body System			
Tissue NOS	(1)	(3)	(3)
Mediastinum, inflammation, chronic active			1 (33%)
Genital System			
Ovary	(49)	(49)	(50)
Abscess			1 (2%)
Angiectasis	2 (4%)	1 (2%)	1 (2%)
Cyst	16 (33%)	18 (37%)	15 (30%)
Cyst, multiple	6 (12%)	6 (12%)	4 (8%)
Hyperplasia, tubular	1 (2%)		
Pigmentation		1 (2%)	
Interstitium, hyperplasia		1 (2%)	
Periovarian tissue, inflammation, chronic active			1 (2%)
Uterus	(50)	(50)	(49)
Angiectasis		2 (4%)	
Fibrosis		1 (2%)	
Hydrometra			1 (2%)
Inflammation, acute		1 (2%)	1 (2%)
Thrombus		1 (2%)	
Cervix, hyperplasia, squamous		3 (6%)	
Cervix, inflammation, acute	1 (2%)	6 (12%)	1 (2%)
Cervix, inflammation, chronic			1 (2%)
Endometrium, hyperplasia, cystic	43 (86%)	44 (88%)	34 (69%)
Serosa, fibrosis	1 (2%)		
Vagina	(4)		(8)
Hyperkeratosis	1 (25%)		
Inflammation, acute			4 (50%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Hematopoietic System			
Bone marrow	(50)	(50)	(50)
Atrophy		1 (2%)	
Myelofibrosis	40 (80%)	36 (72%)	30 (60%)
Pigmentation			1 (2%)
Myeloid cell, hyperplasia			7 (14%)
Lymph node	(44)	(44)	(48)
Iliac, hyperplasia, lymphoid		1 (2%)	
Iliac, hyperplasia, plasma cell		1 (2%)	
Iliac, pigmentation	1 (2%)		
Inguinal, hyperplasia, lymphoid	1 (2%)		
Inguinal, hyperplasia, plasma cell		1 (2%)	
Mandibular, cyst, multiple			1 (2%)
Mandibular, hyperplasia, lymphoid		2 (5%)	1 (2%)
Mediastinal, fibrosis	1 (2%)		
Mediastinal, hyperplasia, lymphoid	3 (7%)		
Mediastinal, hyperplasia, plasma cell	1 (2%)		
Mediastinal, pigmentation	1 (2%)		
Mediastinal, thrombus	1 (2%)		
Mesenteric, angiectasis			1 (2%)
Mesenteric, cyst			1 (2%)
Mesenteric, hyperplasia, lymphoid		1 (2%)	
Pancreatic, hyperplasia, lymphoid		1 (2%)	
Renal, hyperplasia, lymphoid		1 (2%)	
Spleen	(49)	(50)	(48)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	4 (8%)
Hyperplasia, lymphoid	8 (16%)	3 (6%)	5 (10%)
Thrombus			1 (2%)
Capsule, fibrosis	1 (2%)	2 (4%)	
Thymus	(41)	(39)	(43)
Atrophy	1 (2%)	4 (10%)	4 (9%)
Congestion			1 (2%)
Cyst	1 (2%)	2 (5%)	2 (5%)
Ectopic parathyroid gland			1 (2%)
Hyperplasia, lymphoid	1 (2%)		3 (7%)
Integumentary System			
Mammary gland	(47)	(46)	(46)
Inflammation, chronic			1 (2%)
Acinus, hyperplasia		1 (2%)	3 (7%)
Duct, cyst	1 (2%)	1 (2%)	
Duct, hyperplasia	1 (2%)		
Skin	(50)	(50)	(50)
Acanthosis	3 (6%)	10 (20%)	
Cyst	1 (2%)		1 (2%)
Exudate		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	2 (4%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(50)	(50)
Hydrocephalus	1 (2%)		
Mineralization	21 (42%)	23 (46%)	16 (32%)
Meninges, fibrosis			1 (2%)
Meninges, infiltration cellular, lymphocyte	1 (2%)		
Respiratory System			
Lung	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	2 (4%)
Fibrosis, multifocal		1 (2%)	
Fungus	1 (2%)		
Hemorrhage	3 (6%)	2 (4%)	3 (6%)
Inflammation, granulomatous	1 (2%)		
Leukocytosis		1 (2%)	
Thrombus	1 (2%)		
Alveolar epithelium, hyperplasia, focal		2 (4%)	
Alveolus, infiltration cellular, histiocyte	2 (4%)	2 (4%)	4 (8%)
Artery, media, hypertrophy	4 (8%)	2 (4%)	3 (6%)
Bronchus, inflammation, acute	1 (2%)		
Perivascular, infiltration cellular, lymphocyte	3 (6%)	6 (12%)	4 (8%)
Pleura, fibrosis		2 (4%)	
Pleura, inflammation, chronic active			1 (2%)
Nose	(50)	(50)	(50)
Angiectasis		1 (2%)	
Exudate	3 (6%)	10 (20%)	17 (34%)
Inflammation, acute	2 (4%)	3 (6%)	9 (18%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic active			5 (10%)
Olfactory epithelium, metaplasia	1 (2%)	20 (40%)	46 (92%)
Trachea	(50)	(49)	(50)
Inflammation, chronic			1 (2%)
Metaplasia, squamous			1 (2%)
Peritracheal tissue, inflammation, chronic active			1 (2%)
Special Senses System			
None			

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Mercuric Chloride (continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Urinary System			
Kidney	(49)	(50)	(50)
Autolysis			3 (6%)
Cyst			1 (2%)
Hydronephrosis			1 (2%)
Nephropathy	21 (43%)	43 (86%)	42 (84%)
Glomerulus, thrombus	1 (2%)		
Pelvis, mineralization			1 (2%)
Perivascular, infiltration cellular, lymphocyte		1 (2%)	2 (4%)
Renal tubule, necrosis, acute		1 (2%)	
Urinary bladder	(48)	(48)	(47)
Inflammation, acute		1 (2%)	
Inflammation, chronic	1 (2%)	2 (4%)	
Metaplasia, squamous	2 (4%)		
Transitional epithelium, hyperplasia		1 (2%)	

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

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). Mercuric chloride was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). Mercuric chloride was incubated with the *S. typhimurium* tester strains (TA100, TA1535, TA1537, and TA98) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of mercuric chloride. High dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose related, was not reproducible, or was of not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive (+) or weakly positive (+w).

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Mercuric chloride was supplied as a coded aliquot by Radian Corporation. The high dose of mercuric chloride was determined by toxicity. 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 resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to medium containing THG (thymidine, hypoxanthine, and glycine) for 1 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 replicated. Treated cultures contained 6×10^6 cells in a 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with mercuric chloride continued for 4 hours, at which time the medium plus mercuric chloride was removed and the cells were resuspended in 20 mL of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{-/-}$); 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. The test was initially performed without S9; because a clearly positive response was obtained, the test was not repeated with induced S9.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Myhr *et al.* (1985). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for mercuric chloride 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.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1985, 1987). Mercuric chloride was sent to the laboratory as a coded aliquot from Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of mercuric chloride; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with mercuric chloride 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 mercuric chloride was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 1.5 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoescht 33258 and Giemsa. In the SCE test with S9, cells were incubated with mercuric chloride, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no mercuric chloride, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity (+w); increases at two or more doses resulted in a determination that the trial was positive (+). A statistically significant trend ($P<0.05$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with mercuric chloride for 8 hours; Colcemid was added and incubation continued for 2 to 3 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 mercuric chloride and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 8.6 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell-cycle information obtained in the SCE test; since cell-cycle delay was observed in Trial 1, the incubation period was extended from 10.6 hours to 20.8 hours in Trial 2.

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. One-hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. Statistical analyses were conducted on both the dose-response curve and individual dose points. For a single trial, a statistically significant ($P\leq0.05$) difference for one dose point and a significant trend ($P\leq0.015$) were considered weak evidence for a positive response (+w); significant differences for two or more doses

indicated the trial was positive (+). A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987).

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assays for induction of sex-linked recessive lethal (SLRL) mutations and chromosomal translocations were performed as described in Zimmering *et al.* (1985). Mercuric chloride was supplied as a coded aliquot from Radian Corporation. It was assayed in the 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, mercuric chloride was retested by injection into adult males. Because neither route of administration produced a positive result, mercuric chloride was not assayed for induction of reciprocal translocations.

To administer mercuric chloride by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double stick tape; injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of mercuric chloride at a level which would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of mercuric chloride in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of mercuric chloride dissolved in 0.7% saline and were allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier post-meiotic stages). For the larval feeding experiment, Canton-S females and males were mated and eggs were exposed in vials with standard cornmeal food containing mercuric chloride in solvent (5% ethanol) or solvent alone (Valencia *et al.*, 1989) Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five *Basc* females to establish two single-day broods. For both the adult and larval exposure experiments, 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 containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if $P \leq 0.01$ and the mutation frequency in the tested group was greater than 0.10%, or if $P \leq 0.05$ 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 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15%, or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A result was considered negative if the $P \geq 0.10$ or if the frequency in the treatment group was less than 0.10%.

RESULTS

Mercuric chloride (0.003 to 33 μg/plate) was not mutagenic in *S. typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Zeiger *et al.*, 1987) (Table E1).

Mercuric chloride was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells; significant increases in mutant colonies were observed in each of three trials conducted without the addition of S9 activation enzymes (McGregor *et al.*, 1988) (Table E2). The loss of replicate positive control cultures (Trials 2 and 3) did not invalidate the responses observed with the treated cultures.

Mercuric chloride was negative for induction of SCEs in CHO cells in the absence of S9 activation, but a weakly positive response was obtained in this assay when mercuric chloride was tested in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table E3). In each of two trials, a significant increase (>20%) in SCEs was noted only at the highest nonlethal dose tested (8.0 and 8.9 μg/mL, respectively). Mercuric chloride also induced Abs in CHO cells, but the positive responses in this assay occurred in the absence, not the presence, of S9 (Table E4). In the first trial without S9, an increase in Abs occurred at all three concentrations tested (3.98 to 7.95 μg/mL). Harvest time was extended in this second trial without S9 to offset the cell cycle delay produced by mercuric chloride treatment. Many of the cells which exhibited chromosomal damage following exposure to mercuric chloride contained complex chromatid aberrations (rearrangements and translocations) and multiple aberrations, and, therefore, the total number of aberrations observed exceeds the number of cells damaged.

In the Abs assay during the second trial without S9, cell cycle delay required an extended harvest time (20.8 hours), and a significant reduction (40%) in cell confluence was observed. The toxicity of mercuric chloride at the concentrations tested in the Abs assay may be a consideration in the evaluation of these results (Bradley *et al.*, 1987; Galloway *et al.*, 1987). It is unclear what, if any, role cytotoxicity plays in the induction of Abs *in vitro* (Scott *et al.*, 1991). Some chemicals which have been shown to be clastogenic *in vivo* do not produce chromosomal damage *in vitro* unless tested at extremely toxic conditions (as judged by a decrease in clonogenicity and mitotic index). Other chemicals which are excellent inducers of Abs *in vitro* at nontoxic concentrations do not produce Abs *in vivo*. The relationship between cytotoxicity and clastogenicity *in vitro* and *in vivo* is discussed in detail by Scott *et al.* (1991). In conclusion, mercuric chloride has been shown to demonstrate clastogenic activity *in vitro*, and this activity should be considered in interpreting the results of the bioassay and in addressing possible mechanisms of toxicity of the chemical.

Mercuric chloride did not induce sex-linked recessive lethal mutations in germ cells of adult male *D. melanogaster* administered mercuric chloride by feeding (363 ppm) or by injection (360 and 450 ppm) (Table E5).

TABLE E1
Mutagenicity of Mercuric Chloride 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	+10% rat S9 Trial 3
TA100	0.000	136 ± 6.8	144 ± 2.9	118 ± 8.7	148 ± 2.0	118 ± 8.1	126 ± 3.7	150 ± 4.1
	0.003	127 ± 6.6	123 ± 1.9					
	0.010	109 ± 12.3	140 ± 6.7					
	0.030	125 ± 2.2	137 ± 3.5					
	0.100	131 ± 4.7	145 ± 10.1					
	0.300	131 ± 0.9	120 ± 9.6[c]	113 ± 8.8	144 ± 8.8	135 ± 7.2	141 ± 9.4	130 ± 5.7
	1.000			122 ± 9.5	141 ± 2.7	118 ± 6.1	145 ± 6.1	149 ± 12.4
	3.300			105 ± 6.4	151 ± 9.0	130 ± 2.9	134 ± 3.7	148 ± 7.2
	10.000			112 ± 10.3	150 ± 6.6	156 ± 10.9	139 ± 2.9	145 ± 8.8
	33.000			Toxic	190 ± 6.7[c]	Toxic	151 ± 8.4	171 ± 9.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,089 ± 18.3	1,027 ± 14.8	1,024 ± 47.1	1,561 ± 23.2	103 ± 2.8	650 ± 29.5	977 ± 41.3
TA1535	0.000	34 ± 4.4	32 ± 3.2	13 ± 1.2	17 ± 1.2	13 ± 2.0	16 ± 1.2	9 ± 0.3
	0.003	34 ± 3.8	29 ± 3.5					
	0.010	24 ± 2.2	22 ± 2.7					
	0.030	28 ± 3.8	29 ± 1.5					
	0.100	33 ± 2.9	29 ± 3.2					
	0.300	18 ± 0.6[c]	21 ± 4.7[c]	13 ± 0.3	9 ± 1.9	13 ± 1.2	14 ± 2.0	17 ± 2.4
	1.000			15 ± 1.8	9 ± 1.2	14 ± 1.8	15 ± 1.5	14 ± 2.3
	3.300			15 ± 1.5	13 ± 2.3	12 ± 1.9	20 ± 1.3	12 ± 2.3
	10.000			10 ± 0.3	12 ± 3.6	20 ± 0.9	16 ± 2.1	14 ± 2.5
	33.000			12 ± 0.7	8 ± 0.9[c]	Toxic	13 ± 3.0	10 ± 3.2[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		905 ± 50.1	855 ± 12.8	87 ± 8.4	77 ± 3.5	14 ± 2.1	75 ± 5.2	56 ± 8.6
TA1537								
	0.000	5 ± 1.2	8 ± 1.9	4 ± 0.6	11 ± 2.0	8 ± 2.0	7 ± 1.8	10 ± 2.3
	0.003	6 ± 1.3	9 ± 0.7					
	0.010	7 ± 0.3	6 ± 3.1					
	0.030	6 ± 1.7	10 ± 0.7					
	0.100	5 ± 1.5	9 ± 1.2					
	0.300	8 ± 0.9	Toxic	6 ± 1.7	9 ± 1.7	7 ± 1.2	9 ± 0.9	11 ± 1.5
	1.000			6 ± 2.1	9 ± 1.2	7 ± 2.0	9 ± 0.9	13 ± 3.1
	3.300			6 ± 1.5	7 ± 0.7	9 ± 1.2	10 ± 0.3	12 ± 2.4
	10.000			8 ± 0.6	9 ± 1.9	9 ± 1.5	9 ± 2.3	10 ± 0.6
	33.000			Toxic	12 ± 1.5[c]	Toxic	7 ± 2.1	9 ± 0.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		332 ± 104.8	197 ± 16.6	87 ± 1.0	133 ± 7.8	7 ± 1.2	63 ± 10.1	77 ± 3.8

TABLE E1
Mutagenicity of Mercuric Chloride in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% hamster S9 Trial 3
TA98							
	0.000	53 ± 5.0	20 ± 1.2	22 ± 1.5	71 ± 3.7	32 ± 0.9	19 ± 1.2
	0.003	47 ± 3.0	21 ± 1.7	23 ± 5.8			
	0.010	53 ± 3.2	17 ± 2.3	20 ± 0.6			
	0.030	54 ± 2.9	23 ± 4.0	20 ± 2.1			
	0.100	55 ± 1.8	21 ± 1.5	27 ± 1.8			
	0.300	19 ± 3.6[c]	14 ± 0.6[c]	Toxic	62 ± 8.3	28 ± 3.0	30 ± 0.9
	1.000				58 ± 8.2	31 ± 3.0	25 ± 1.2
	3.300				67 ± 2.9	30 ± 0.9	26 ± 5.2
	10.000				58 ± 2.6	27 ± 1.5	20 ± 2.8
	33.000				Toxic	24 ± 2.3	15 ± 0.6[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,870 ± 24.6	1,298 ± 54.5	1,215 ± 50.3	774 ± 36.7	877 ± 6.0	1,418 ± 72.8

TA98 (continued)

	+ 10% rat S9 Trial 1	+ 10% rat S9 Trial 2	+ 10% rat S9 Trial 3
0.000	60 ± 6.2	28 ± 0.6	31 ± 0.3
0.003			
0.010			
0.030			
0.100			
0.300	44 ± 4.2	25 ± 3.2	29 ± 2.4
1.000	46 ± 3.8	24 ± 1.9	28 ± 3.3
3.300	49 ± 3.2	22 ± 3.5	30 ± 2.9
10.000	43 ± 5.6	25 ± 4.2	26 ± 2.6
33.000	Toxic	21 ± 1.2	21 ± 4.5[c]
Trial summary	Negative	Negative	Negative
Positive control	68 ± 8.4	434 ± 22.6	758 ± 43.0

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Zeiger *et al.* (1987).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] Slight toxicity
[d] 2-aminoanthracene was used on 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 Mercuric Chloride[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Dimethylsulfoxide						
		70	103	92	39	
		70	104	87	42	
		68	92	93	46	
		61	101	104	56	46
Methyl methanesulfonate						
		24	16	183	260	
	15.0	28	22	258	311	285*
Mercuric chloride						
	0.1	66	53	60	30	
		60	56	75	42	36
	0.2	56	47	107	64	
		68	51	141	69	67
	0.4	62	23	159	86	
		63	19	156	83	84*
	0.8	48	6	299	208	
		46	7	305	222	215*
	1.6	Lethal				
		Lethal				
Trial 2						
Dimethylsulfoxide						
		83	95	129	52	
		85	109	161	63	
		71	95	97	46	54
Methyl methanesulfonate						
	15.0000	20	20	200	333	
Mercuric chloride						
	0.2107	66	37	185	93	
		85	45	197	77	85*
	0.316	74	49	140	63	
		106	50	135	42	53
	0.4741	69	21	128	62	
		103	33	137	44	53
	0.7111	67	13	201	100	
	1.067	75	12	217	96	
		73	10	222	102	99
	1.6	Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by Mercuric Chloride
(continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Dimethylsulfoxide						
		54	99	95	58	
		79	112	86	36	
		70	89	111	53	49
Methyl methanesulfonate						
	15.0	17	16	236	467	
Mercuric chloride						
	0.1	56	65	98	59	
		60	58	100	56	57
	0.3	59	39	111	62	
		52	36	69	44	53
	0.5	60	13	217	121	
		61	20	221	121	121*
	0.7	64	22	207	108	
	0.9	65	9	276	141	

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Inveresk Research International. The experimental protocol and these data are presented in detail by McGregor *et al.* (1988).
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 x 10^6 cells treated).
[c] Mean from three replicate plates of approximately 1/3 (3 x 10^6) cells each

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

Compound	Dose μg/mL	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,027	501	0.48	10.0	25.6	
Mitomycin-C	0.01	5	100	182	1.82	36.4	25.6	273.09
Mercuric chloride	3.50	50	1,020	523	0.51	10.5	25.6	5.11
	6.00	50	1,028	579	0.56	11.6	25.6	15.46
								P=0.009[c]
Trial 2								
Summary: Negative								
Dimethylsulfoxide		50	1,031	439	0.42	8.8	25.5	
Mitomycin-C	1	50	1,026	579	0.56	11.6	25.5	32.53
	10	5	105	203	1.93	40.6	25.5	354.05
Mercuric chloride	3	50	1,042	432	0.41	8.6	25.5	-2.64
	4	50	1,035	436	0.42	8.7	25.5	-1.07
	5	50	1,031	464	0.45	9.3	30.3[d]	5.69
								P=0.200
+S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,028	480	0.46	9.6	26	
Cyclophosphamide	2	5	101	194	1.92	38.8	26	311.37
Mercuric chloride	3	50	1,020	517	0.50	10.3	26	8.55
	8	50	1,018	596	0.58	11.9	26	25.39*
								P<0.001

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Mercuric Chloride
(continued)

Compound	Dose μg/mL	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-somes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)
+S9 (continued)								
Trial 2								
Summary: Weak positive								
Dimethylsulfoxide		50	1,042	417	0.40	8.3	26	
Cyclophosphamide	0.30	50	1,039	576	0.55	11.5	26	38.53
	2.00	5	104	174	1.67	34.8	26	318.07
Mercuric chloride	5.00	50	1,037	445	0.42	8.9	26	7.23
	7.00	50	1,044	428	0.40	8.6	26	2.44
	8.90	50	1,034	497	0.48	9.9	26	20.11*
								P=0.010

* Positive (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987).
[b] Percent increase in SCEs/chromosome of culture exposed to mercuric chloride relative to those of culture exposed to solvent.
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[d] Because mercuric chloride induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second division cells available for analysis.

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Mercuric Chloride[a]

-S9					+S9				
Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs	Dose µg/mL	Total Cells	No. of Abs	Abs/ Cell	Percent Cells w/Abs
Trial 1 – Harvest time: 10.6 hours Summary: Weak positive					**Trial 1** – Harvest time: 10.6 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
100	100	0	0.00	0.0	100	100	1	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.50	50	13	0.26	22.0	25.00	50	9	0.18	10.0
Mercuric chloride					Mercuric chloride				
3.98	100	2	0.02	2.0	5.01	100	1	0.01	1.0
6.03	100	0	0.00	0.0	7.47	100	0	0.00	0.0
7.95	100	10	0.10	7.0*	10.01	100	0	0.00	0.0
				P=0.004[b]					P=0.902
Trial 2 – Harvest time: 20.8 hours[c] Summary: Positive									
Dimethylsulfoxide									
100	100	0	0.00	0.0					
Mitomycin-C									
0.05	50	16	0.32	24.0					
Mercuric chloride									
6.03	100	23	0.23	8.0*					
7.02	100	49	0.49	20.0*					
8.04	100	89	0.89	39.0*					
				P≤0.000					

* Positive (P≤0.05)
[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987).
[b] Significance of relative percent cells with Abs tested by the linear regression trend test vs. log of the dose
[c] Because mercuric chloride induced significant cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphases at harvest.

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

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			
				Mating 1	Mating 2	Mating 3	Total[b]
Injection	360	20	15	1/1,003	0/1,009	0/1,018	1/3,030 (0.03%)
	0			0/989	0/947	1/986	1/2,922 (0.03%)
Feeding	363	34	20	2/2,244	3/1,898	2/1,851	7/5,993 (0.12%)
	0			0/1,984	1/1,922	2/1,946	3/5,852 (0.05%)
Injection	450	17	0	2/941	1/962	0/1,006	3/2,909 (0.10%)
	0			1/938	0/724	1/1,003	2/2,665 (0.08%)

[a] Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering *et al.* (1985).
[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 F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	1.25 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
Male						
n	5	5	5	5	5	3
Necropsy body wt	178 ± 8	186 ± 7	184 ± 10	180 ± 6	167 ± 3	156 ± 10
Brain						
Absolute	1.64 ± 0.01	1.65 ± 0.02	1.73 ± 0.02	1.71 ± 0.05	1.69 ± 0.03	1.65 ± 0.02
Relative	9.27 ± 0.44	8.92 ± 0.28	9.49 ± 0.55	9.58 ± 0.48	10.16 ± 0.35	10.62 ± 0.48
Heart						
Absolute	0.77 ± 0.04	0.76 ± 0.05	0.80 ± 0.05	0.75 ± 0.04	0.73 ± 0.01	0.71 ± 0.03
Relative	4.35 ± 0.10	4.09 ± 0.16	4.38 ± 0.21	4.20 ± 0.16	4.37 ± 0.15	4.61 ± 0.35
R. Kidney						
Absolute	0.86 ± 0.05	0.99 ± 0.03	1.03 ± 0.04*	1.03 ± 0.06*	1.11 ± 0.08**[b]	1.08 ± 0.12*
Relative	4.83 ± 0.16	5.36 ± 0.17	5.63 ± 0.10*	5.74 ± 0.16**	6.54 ± 0.46**[b]	6.89 ± 0.32**
Liver						
Absolute	7.42 ± 0.29	7.44 ± 0.20	8.14 ± 0.39	7.44 ± 0.46	6.96 ± 0.21	6.59 ± 0.49
Relative	41.7 ± 0.9	40.2 ± 1.6	44.3 ± 1.0	41.3 ± 1.3	41.7 ± 1.4	42.2 ± 0.9
Lung						
Absolute	1.02 ± 0.09	1.00 ± 0.04	1.05 ± 0.09	1.03 ± 0.08	1.01 ± 0.04	0.85 ± 0.05
Relative	5.69 ± 0.31	5.37 ± 0.19	5.67 ± 0.34	5.70 ± 0.35	6.01 ± 0.16	5.41 ± 0.01
Thymus						
Absolute	0.35 ± 0.02	0.40 ± 0.02	0.40 ± 0.01	0.35 ± 0.02	0.34 ± 0.04	0.28 ± 0.01
Relative	1.97 ± 0.07	2.14 ± 0.07	2.20 ± 0.14	1.96 ± 0.12	2.07 ± 0.23	1.78 ± 0.10
Female						
n	5	5	5	5	5	5
Necropsy body wt	130 ± 3	131 ± 3	127 ± 5	128 ± 3	125 ± 2	116 ± 2**
Brain						
Absolute	1.59 ± 0.04	1.67 ± 0.04	1.64 ± 0.06	1.57 ± 0.03	1.67 ± 0.04	1.56 ± 0.05
Relative	12.2 ± 0.1	12.8 ± 0.4	12.9 ± 0.4	12.3 ± 0.4	13.3 ± 0.4	13.4 ± 0.5*
Heart						
Absolute	0.61 ± 0.02	0.60 ± 0.02	0.61 ± 0.03	0.59 ± 0.02	0.61 ± 0.01	0.53 ± 0.02*
Relative	4.68 ± 0.21	4.60 ± 0.20	4.79 ± 0.14	4.64 ± 0.19	4.88 ± 0.15	4.52 ± 0.12
R. Kidney						
Absolute	0.61 ± 0.01	0.70 ± 0.02	0.70 ± 0.03	0.82 ± 0.10*	0.79 ± 0.03*	0.78 ± 0.03*
Relative	4.67 ± 0.10	5.38 ± 0.15	5.52 ± 0.14	6.46 ± 0.94**	6.27 ± 0.19**	6.67 ± 0.26**
Liver						
Absolute	5.41 ± 0.09	5.37 ± 0.17	5.23 ± 0.15	5.13 ± 0.17	5.29 ± 0.10	4.80 ± 0.14**
Relative	41.5 ± 0.7	41.1 ± 1.1	41.1 ± 1.0	40.1 ± 1.1	42.2 ± 0.7	41.3 ± 1.3
Lung						
Absolute	0.84 ± 0.03	0.86 ± 0.02	0.84 ± 0.02	0.83 ± 0.03[b]	0.84 ± 0.02	0.75 ± 0.02**
Relative	6.45 ± 0.25	6.60 ± 0.21	6.59 ± 0.28	6.40 ± 0.26[b]	6.68 ± 0.14	6.46 ± 0.12
Thymus						
Absolute	0.34 ± 0.03	0.33 ± 0.01	0.34 ± 0.02	0.34 ± 0.01	0.33 ± 0.01	0.28 ± 0.01**
Relative	2.62 ± 0.23	2.53 ± 0.07	2.66 ± 0.10	2.63 ± 0.06	2.59 ± 0.08	2.37 ± 0.10

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	0.312 mg/kg	0.625 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
n	10	10	10	10	10	10
Male						
Necropsy body wt	442 ± 9	441 ± 5	422 ± 9	431 ± 9	428 ± 9	413 ± 10*
Brain						
Absolute	1.99 ± 0.03	1.95 ± 0.04	1.91 ± 0.03	1.95 ± 0.04	1.97 ± 0.04[b]	1.91 ± 0.04
Relative	4.49 ± 0.05	4.42 ± 0.08	4.55 ± 0.11	4.54 ± 0.06	4.65 ± 0.12[b]	4.64 ± 0.09
Heart						
Absolute	1.26 ± 0.04	1.28 ± 0.03	1.27 ± 0.04	1.26 ± 0.05	1.27 ± 0.04	1.20 ± 0.03
Relative	2.84 ± 0.07	2.90 ± 0.04	3.00 ± 0.07	2.92 ± 0.09	2.97 ± 0.07	2.92 ± 0.06
R. Kidney						
Absolute	1.62 ± 0.04	1.79 ± 0.03*	1.83 ± 0.05**	1.87 ± 0.06*	1.87 ± 0.06*	1.72 ± 0.06*
Relative	3.67 ± 0.07	4.05 ± 0.06**	4.34 ± 0.06**	4.34 ± 0.12**	4.38 ± 0.08**	4.17 ± 0.09**
Liver						
Absolute	17.20 ± 0.45	16.67 ± 0.26	16.51 ± 0.46	16.60 ± 0.48	17.21 ± 0.44	15.79 ± 0.47
Relative	38.9 ± 0.9	37.9 ± 0.8	39.1 ± 0.7	38.6 ± 0.9	40.2 ± 0.6	38.3 ± 0.5
Lung						
Absolute	1.80 ± 0.10	1.76 ± 0.05	1.80 ± 0.06	1.78 ± 0.08	1.74 ± 0.03	1.82 ± 0.09
Relative	4.08 ± 0.23	3.99 ± 0.09	4.29 ± 0.15	4.14 ± 0.15	4.09 ± 0.09	4.40 ± 0.18
R. Testis						
Absolute	1.61 ± 0.03	1.57 ± 0.03	1.58 ± 0.06	1.58 ± 0.04	1.58 ± 0.04	1.60 ± 0.02
Relative	3.65 ± 0.05	3.56 ± 0.08	3.74 ± 0.09	3.68 ± 0.08	3.71 ± 0.08	3.90 ± 0.06*
Thymus						
Absolute	0.20 ± 0.01[b]	0.22 ± 0.01	0.21 ± 0.02	0.23 ± 0.02	0.22 ± 0.01	0.22 ± 0.02
Relative	0.46 ± 0.02[b]	0.49 ± 0.02	0.51 ± 0.04	0.53 ± 0.04	0.51 ± 0.02	0.52 ± 0.04
Female						
Necropsy body wt	242 ± 4	231 ± 4	233 ± 3	227 ± 5**	224 ± 3**	228 ± 4**
Brain						
Absolute	1.81 ± 0.02	1.80 ± 0.03	1.81 ± 0.03	1.79 ± 0.03	1.85 ± 0.03	1.91 ± 0.02*
Relative	7.51 ± 0.13	7.79 ± 0.14	7.77 ± 0.13	7.92 ± 0.16*	8.29 ± 0.15**	8.41 ± 0.10**
Heart						
Absolute	0.89 ± 0.03	0.81 ± 0.03*	0.80 ± 0.02*	0.82 ± 0.02*	0.78 ± 0.02*	0.81 ± 0.03*
Relative	3.67 ± 0.08	3.48 ± 0.11	3.45 ± 0.09	3.61 ± 0.08	3.50 ± 0.11	3.58 ± 0.10
R. Kidney						
Absolute	0.92 ± 0.02	0.95 ± 0.03	1.00 ± 0.01*	1.01 ± 0.03*	1.02 ± 0.03*	1.05 ± 0.03**
Relative	3.80 ± 0.07	4.09 ± 0.10*	4.29 ± 0.05**	4.46 ± 0.09**	4.57 ± 0.11**	4.62 ± 0.11**
Liver						
Absolute	9.22 ± 0.18	8.84 ± 0.22	9.05 ± 0.47	8.37 ± 0.30	8.25 ± 0.23	9.34 ± 0.23
Relative	38.1 ± 0.7	38.3 ± 1.0	38.7 ± 1.9	36.8 ± 1.1	36.9 ± 0.8	41.1 ± 0.8
Lung						
Absolute	1.27 ± 0.02	1.38 ± 0.07	1.32 ± 0.03	1.29 ± 0.05	1.21 ± 0.05	1.29 ± 0.03
Relative	5.25 ± 0.06	5.96 ± 0.25*	5.66 ± 0.13	5.68 ± 0.16	5.42 ± 0.20	5.66 ± 0.08
Thymus						
Absolute	0.20 ± 0.02	0.19 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.18 ± 0.01	0.19 ± 0.01
Relative	0.84 ± 0.06	0.84 ± 0.06	0.74 ± 0.04	0.83 ± 0.02	0.80 ± 0.03	0.83 ± 0.04

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	2.5 mg/kg	5 mg/kg
n	10	10	10
Male			
Necropsy body wt	441 ± 13	406 ± 6*	416 ± 8
Brain			
Absolute	2.05 ± 0.03	2.09 ± 0.02	2.03 ± 0.04
Relative	4.68 ± 0.10	5.15 ± 0.11*	4.90 ± 0.15
R. Kidney			
Absolute	1.62 ± 0.07	1.79 ± 0.04	1.76 ± 0.06
Relative	3.68 ± 0.13	4.40 ± 0.10**	4.24 ± 0.17**
Liver			
Absolute	13.40 ± 0.49	12.39 ± 0.49	13.23 ± 0.39
Relative	30.3 ± 0.5	30.5 ± 1.1	31.9 ± 0.8
Female			
Necropsy body wt	287 ± 4	259 ± 7**	249 ± 7**
Brain			
Absolute	1.87 ± 0.04	1.91 ± 0.03	1.91 ± 0.02
Relative	6.53 ± 0.18	7.38 ± 0.10**	7.72 ± 0.22**
R. Kidney			
Absolute	1.07 ± 0.08	1.14 ± 0.04	1.10 ± 0.03
Relative	3.71 ± 0.27	4.39 ± 0.11*	4.42 ± 0.08**
Liver			
Absolute	8.23 ± 0.17	7.72 ± 0.21	7.66 ± 0.20*
Relative	28.7 ± 0.5	29.8 ± 0.5	30.9 ± 0.6**

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg[b]
Male						
n	5	5	5	5	4	
Necropsy body wt	20.2 ± 0.7	20.0 ± 0.3	20.4 ± 0.7	21.2 ± 0.8	19.8 ± 1.3	
Brain						
Absolute	0.43 ± 0.01	0.43 ± 0.01	0.43 ± 0.00	0.44 ± 0.02	0.43 ± 0.02	
Relative	21.5 ± 0.6	21.7 ± 0.5	20.9 ± 0.7	20.8 ± 0.7	21.7 ± 0.8	
Heart						
Absolute	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.00	
Relative	6.19 ± 0.30	6.64 ± 0.49	6.54 ± 0.28	6.22 ± 0.46	6.81 ± 0.45	
R. Kidney						
Absolute	0.17 ± 0.01	0.21 ± 0.01*	0.22 ± 0.01*	0.25 ± 0.01**	0.23 ± 0.02**	
Relative	8.65 ± 0.27	10.46 ± 0.34**	10.79 ± 0.32**	11.96 ± 0.65**	11.37 ± 0.54**	
Liver						
Absolute	0.84 ± 0.05	0.84 ± 0.02	0.81 ± 0.04	0.82 ± 0.03	0.79 ± 0.07	
Relative	41.3 ± 1.5	42.2 ± 1.6	40.0 ± 2.0	38.7 ± 0.6	39.9 ± 1.2	
Lung						
Absolute	0.16 ± 0.01	0.16 ± 0.00	0.17 ± 0.01	0.19 ± 0.01	0.16 ± 0.01	
Relative	8.14 ± 0.56	8.21 ± 0.24	8.34 ± 0.46	8.92 ± 0.53	8.01 ± 0.43	
Thymus[c]						
Absolute	23.80 ± 4.35	20.20 ± 1.56	15.80 ± 2.35	26.20 ± 4.43	18.50 ± 5.58	
Relative	1.21 ± 0.27	1.01 ± 0.08	0.77 ± 0.11	1.22 ± 0.19	0.92 ± 0.25	
Female						
n	5	5	5	5	5	1[d]
Necropsy body wt	17.2 ± 0.2	16.4 ± 0.2	16.4 ± 0.2	16.8 ± 0.4	16.4 ± 0.5	16.0
Brain						
Absolute	0.41 ± 0.01	0.42 ± 0.02	0.45 ± 0.01*	0.44 ± 0.01	0.44 ± 0.00	0.43
Relative	23.8 ± 0.8	25.4 ± 1.2	27.7 ± 0.5*	26.3 ± 0.5*	26.9 ± 0.7*	26.9
Heart						
Absolute	0.10 ± 0.01	0.11 ± 0.00	0.12 ± 0.01	0.11 ± 0.01	0.10 ± 0.00	0.10
Relative	6.04 ± 0.39	6.84 ± 0.30	7.47 ± 0.54*	6.50 ± 0.36	6.35 ± 0.09	6.00
R. Kidney						
Absolute	0.13 ± 0.01	0.15 ± 0.01	0.16 ± 0.00	0.15 ± 0.01	0.16 ± 0.01*	0.21
Relative	7.68 ± 0.32	9.20 ± 0.83*	9.79 ± 0.30*	9.15 ± 0.49*	9.90 ± 0.26**	12.81
Liver						
Absolute	0.74 ± 0.02	0.74 ± 0.04	0.70 ± 0.03	0.69 ± 0.02	0.62 ± 0.05*	0.64
Relative	43.0 ± 1.0	45.2 ± 2.6	42.8 ± 1.7	41.3 ± 0.6	37.7 ± 1.9*	40.2
Lung						
Absolute	0.15 ± 0.01	0.16 ± 0.02	0.14 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.15
Relative	8.54 ± 0.47	9.99 ± 0.87	8.42 ± 0.25	9.86 ± 0.32	9.77 ± 0.58	9.31
Thymus[c]						
Absolute	35.00 ± 2.55	29.00 ± 4.55	28.40 ± 3.20	25.00 ± 2.30*	25.60 ± 1.91*	15.00
Relative	2.03 ± 0.13	1.78 ± 0.29	1.73 ± 0.19	1.48 ± 0.11	1.56 ± 0.11	0.94

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] No data collected for males due to 100% mortality in this group.
[c] Organ weights are given in milligrams.
[d] No standard error calculated for 80 mg/kg females due to high mortality in this group.

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	1.25 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
n	10	10	10	9	10	10
Male						
Necropsy body wt	34.4 ± 1.0	35.7 ± 1.1	34.8 ± 1.3	36.6 ± 1.3	31.4 ± 0.7	30.5 ± 0.9*
Brain						
Absolute	0.48 ± 0.01	0.46 ± 0.00	0.45 ± 0.01	0.47 ± 0.02	0.44 ± 0.01**	0.45 ± 0.01**
Relative	14.1 ± 0.4	12.9 ± 0.4	13.1 ± 0.6	13.1 ± 0.6	14.1 ± 0.30	14.7 ± 0.4
Heart						
Absolute	0.20 ± 0.02	0.19 ± 0.01	0.18 ± 0.01	0.20 ± 0.01	0.17 ± 0.01*	0.17 ± 0.01*
Relative	5.83 ± 0.39	5.39 ± 0.15	5.07 ± 0.28	5.38 ± 0.25	5.31 ± 0.18	5.59 ± 0.22
R. Kidney						
Absolute	0.32 ± 0.01	0.32 ± 0.01	0.33 ± 0.01	0.38 ± 0.01**	0.38 ± 0.01**	0.42 ± 0.02**
Relative	9.34 ± 0.19	9.11 ± 0.22	9.58 ± 0.41	10.45 ± 0.32	12.30 ± 0.54**	13.62 ± 0.50**
Liver						
Absolute	1.78 ± 0.07	1.62 ± 0.06	1.57 ± 0.05	1.72 ± 0.05	1.53 ± 0.04**	1.57 ± 0.06*
Relative	51.7 ± 1.2	45.4 ± 0.9**	45.3 ± 1.2**	47.3 ± 1.5	48.7 ± 0.8	51.5 ± 1.53
Lung						
Absolute	0.27 ± 0.02	0.26 ± 0.01	0.25 ± 0.01	0.26 ± 0.02	0.23 ± 0.01	0.24 ± 0.01
Relative	7.85 ± 0.53	7.31 ± 0.23	7.17 ± 0.31	7.11 ± 0.47	7.46 ± 0.53	8.02 ± 0.53
R. Testis						
Absolute	0.11 ± 0.01	0.12 ± 0.00	0.12 ± 0.00	0.13 ± 0.00	0.11 ± 0.01	0.12 ± 0.00
Relative	3.32 ± 0.12	3.32 ± 0.18	3.41 ± 0.15	3.52 ± 0.11	3.63 ± 0.17	3.85 ± 0.10*
Thymus[b]						
Absolute	35.10 ± 1.68	33.90 ± 1.82	38.11 ± 2.31[c]	30.22 ± 2.39	34.40 ± 2.49	32.70 ± 2.86
Relative	1.03 ± 0.06	0.96 ± 0.06	1.13 ± 0.10[c]	0.83 ± 0.06	1.10 ± 0.08	1.08 ± 0.10
Female						
Necropsy body wt	27.0 ± 1.0	27.0 ± 1.2	27.5 ± 1.2	26.9 ± 1.3	25.0 ± 0.8	26.9 ± 1.0
Brain						
Absolute	0.49 ± 0.01	0.47 ± 0.00*	0.47 ± 0.01*	0.46 ± 0.01**	0.45 ± 0.01**	0.47 ± 0.01**
Relative	18.4 ± 0.8	17.6 ± 0.7	17.2 ± 0.7	17.4 ± 0.7	18.3 ± 0.6	17.6 ± 0.5
Heart						
Absolute	0.14 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.12 ± 0.00
Relative	5.07 ± 0.21	5.07 ± 0.32	5.31 ± 0.23	5.33 ± 0.29	5.20 ± 0.18	4.51 ± 0.17
R. Kidney						
Absolute	0.21 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.23 ± 0.02	0.20 ± 0.01	0.22 ± 0.01
Relative	7.66 ± 0.28	7.39 ± 0.14	7.46 ± 0.16	8.34 ± 0.31	8.12 ± 0.20	8.00 ± 0.21
Liver						
Absolute	1.40 ± 0.07	1.23 ± 0.05	1.24 ± 0.05	1.34 ± 0.07	1.18 ± 0.04*	1.30 ± 0.05
Relative	51.7 ± 1.1	45.9 ± 1.6**	45.3 ± 0.7**	50.0 ± 0.7	47.4 ± 1.0	48.5 ± 1.9
Lung						
Absolute	0.18 ± 0.01	0.20 ± 0.01	0.25 ± 0.03**	0.19 ± 0.01	0.20 ± 0.01	0.19 ± 0.01
Relative	6.77 ± 0.24	7.65 ± 0.38	8.87 ± 0.67**	7.15 ± 0.36	8.11 ± 0.34	7.20 ± 0.26
Thymus[b]						
Absolute	42.60 ± 2.38	38.10 ± 2.86	38.30 ± 2.13	43.78 ± 2.44	42.30 ± 2.88	47.30 ± 4.42
Relative	1.58 ± 0.07	1.42 ± 0.10	1.41 ± 0.09	1.64 ± 0.09	1.69 ± 0.11	1.79 ± 0.20

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] Organ weights are given in milligrams.
[c] n=9

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
n	10	10	10
Male			
Necropsy body wt	34.4 ± 1.2	35.3 ± 1.1	32.0 ± 1.4
Brain			
Absolute	0.44 ± 0.00	0.45 ± 0.01	0.44 ± 0.01
Relative	12.9 ± 0.4	12.7 ± 0.4	14.0 ± 0.6
R. Kidney			
Absolute	0.33 ± 0.02	0.40 ± 0.02*	0.42 ± 0.02**
Relative	9.66 ± 0.36	11.39 ± 0.59	13.46 ± 0.79**
Liver			
Absolute	1.38 ± 0.09	1.27 ± 0.03	1.27 ± 0.06
Relative	40.0 ± 1.8	36.3 ± 1.1	39.7 ± 1.0
Female			
Necropsy body wt	32.4 ± 1.2	29.9 ± 1.7	28.9 ± 1.3
Brain			
Absolute	0.45 ± 0.01	0.45 ± 0.01	0.45 ± 0.01
Relative	14.2 ± 0.5	15.4 ± 0.8	15.7 ± 0.8
R. Kidney			
Absolute	0.20 ± 0.01	0.23 ± 0.01	0.23 ± 0.01
Relative	6.23 ± 0.22	7.71 ± 0.33*	7.98 ± 0.54**
Liver			
Absolute	1.15 ± 0.04	1.14 ± 0.03	1.07 ± 0.04
Relative	35.7 ± 0.7	38.9 ± 1.6	37.1 ± 1.2

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

APPENDIX G
CLINICAL CHEMISTRY AND URINALYSIS RESULTS

TABLE G1
Clinical Chemistry Data for Rats in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	0.312 mg/kg	1.25 mg/kg	5 mg/kg
Male				
n	10	10	10	10
Blood urea nitrogen (mg/dL)				
2 months	14.5 ± 0.4	14.4 ± 0.4	14.8 ± 0.5	15.1 ± 0.7
4 months	15.6 ± 0.3	15.1 ± 0.3	15.7 ± 0.5[b]	15.6 ± 0.4
6 months	15.1 ± 0.3	14.9 ± 0.4	15.0 ± 0.5	15.3 ± 0.5
Creatinine (mg/dL)				
2 months	0.60 ± 0.03	0.56 ± 0.02	0.57 ± 0.02	0.54 ± 0.03
4 months	0.69 ± 0.01	0.58 ± 0.02**	0.57 ± 0.02**[b]	0.63 ± 0.02**
6 months	0.70 ± 0.03	0.61 ± 0.04	0.65 ± 0.06	0.62 ± 0.03
Sodium (meq/L)				
2 months	147 ± 1	145 ± 3	149 ± 1	149 ± 1
4 months	149 ± 1	150 ± 1	150 ± 1[b]	149 ± 1
Potassium (meq/L)				
2 months	5.49 ± 0.05	5.56 ± 0.20	5.67 ± 0.16	5.82 ± 0.22
4 months	5.64 ± 0.09	5.24 ± 0.06**	5.39 ± 0.06*[b]	5.21 ± 0.07**
Chloride (meq/L)				
2 months	107 ± 2	104 ± 2	107 ± 1*	107 ± 0*
4 months	108 ± 1	109 ± 1	109 ± 1[b]	108 ± 1
Calcium (mg/dL)				
2 months	11.1 ± 0.1	11.1 ± 0.1	10.9 ± 0.1	10.9 ± 0.2
4 months	10.8 ± 0.1	10.6 ± 0.1	10.5 ± 0.1*[b]	10.4 ± 0.1**
Inorganic phosphorus (mg/dL)				
2 months	7.5 ± 0.1	7.6 ± 0.2	7.9 ± 0.1*	8.2 ± 0.2**
4 months	6.3 ± 0.1	6.3 ± 0.1	6.4 ± 0.1[b]	6.5 ± 0.1
Total protein (g/dL)				
2 months	7.1 ± 0.1	7.2 ± 0.1	7.2 ± 0.1	7.4 ± 0.1
4 months	7.6 ± 0.1	7.4 ± 0.1	7.4 ± 0.1[b]	7.4 ± 0.1
6 months	7.4 ± 0.1	7.4 ± 0.2	7.4 ± 0.3	7.4 ± 0.2
Albumin (g/dL)				
2 months	3.8 ± 0.0	3.8 ± 0.1	3.7 ± 0.1	3.8 ± 0.0
4 months	3.8 ± 0.0	3.8 ± 0.0	3.7 ± 0.0*[b]	3.6 ± 0.0**
Albumin/globulin ratio				
2 months	1.13 ± 0.02	1.13 ± 0.02	1.10 ± 0.03	1.05 ± 0.02*
4 months	1.01 ± 0.02	1.02 ± 0.03	1.00 ± 0.02[b]	0.97 ± 0.03
Total bilirubin (mg/dL)				
2 months	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
4 months	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0[b]	0.1 ± 0.0

TABLE G1
Clinical Chemistry Data for Rats in the 6-Month Gavage Studies of Mercuric Chloride (continued)

	Vehicle Control	0.312 mg/kg	1.25 mg/kg	5 mg/kg
Male (continued)				
n	10	10	10	10
Acid phosphatase (IU/L)				
2 months	30 ± 3	33 ± 4	38 ± 5	29 ± 3
4 months	153 ± 13	130 ± 12	141 ± 22	189 ± 17
6 months	194 ± 13	219 ± 19	203 ± 10	206 ± 16
Alkaline phosphatase (IU/L)				
2 months	110 ± 14	96 ± 12	91 ± 14	94 ± 11
4 months	701 ± 192	558 ± 159	458 ± 87	1,440 ± 152*
6 months	679 ± 76	689 ± 86	619 ± 51	784 ± 98
Alanine aminotransferase (IU/L)				
2 months	45 ± 1	49 ± 2	46 ± 2	47 ± 2
4 months	41 ± 2	36 ± 1**	37 ± 1*[b]	34 ± 1**[b]
6 months	49 ± 2	56 ± 4	49 ± 2	51 ± 3
Aspartate aminotransferase (IU/L)				
2 months	80 ± 3	82 ± 3	79 ± 3	82 ± 4
4 months	72 ± 2	61 ± 1**	61 ± 2**[b]	64 ± 2**
Lactate dehydrogenase (IU/L)				
2 months	484 ± 62	467 ± 47	460 ± 63	506 ± 57
4 months	528 ± 20	442 ± 25	436 ± 33[b]	536 ± 42
6 months	625 ± 84	586 ± 66	624 ± 85	576 ± 92
Ornithine carbamoyltransferase (IU/L)				
2 months	5 ± 1	6 ± 1[c]	4 ± 1[d]	5 ± 1[d]
4 months	8 ± 2[b]	6 ± 2	6 ± 1[b]	7 ± 1[d]
Sorbitol dehydrogenase (IU/L)				
2 months	18 ± 1	22 ± 1	20 ± 0	19 ± 2
4 months	19 ± 1	19 ± 1	19 ± 1[b]	18 ± 1
6 months	13 ± 1	16 ± 1	14 ± 1	14 ± 1
Serum cholinesterase (IU/L)				
2 months	907.5 ± 17.0	912.8 ± 14.5	919.0 ± 24.0	933.4 ± 31.9
4 months	837.2 ± 17.9	839.9 ± 23.6	838.9 ± 16.6[b]	856.3 ± 33.4
6 months	792.7 ± 12.6	837.0 ± 19.1	826.2 ± 23.3	855.5 ± 24.4*
pH				
2 months	7.60 ± 0.40	7.30 ± 0.42	7.10 ± 0.43	7.80 ± 0.36
4 months	6.70 ± 0.33	6.50 ± 0.31	7.00 ± 0.26	7.20 ± 0.33

TABLE G1
Clinical Chemistry Data for Rats in the 6-Month Gavage Studies of Mercuric Chloride (continued)

	Vehicle Control	0.312 mg/kg	1.25 mg/kg	5 mg/kg
Female				
n	10	10	10	10
Blood urea nitrogen (mg/dL)				
2 months	15.6 ± 0.4	15.5 ± 0.3	15.0 ± 0.4	13.9 ± 0.5**
4 months	15.4 ± 0.5	16.1 ± 0.5	15.7 ± 0.5	15.1 ± 0.6
6 months	17.7 ± 0.6	15.8 ± 0.5	16.8 ± 0.4	15.7 ± 0.5*
Creatinine (mg/dL)				
2 months	0.60 ± 0.02	0.59 ± 0.03	0.59 ± 0.04	0.55 ± 0.03
4 months	0.66 ± 0.02	0.62 ± 0.02	0.63 ± 0.02	0.63 ± 0.02
6 months	0.61 ± 0.02	0.54 ± 0.02*	0.56 ± 0.02*	0.54 ± 0.02*
Sodium (meq/L)				
2 months	147 ± 1	148 ± 1	147 ± 0	148 ± 1
4 months	149 ± 2	148 ± 1	149 ± 1	149 ± 1
Potassium (meq/L)				
2 months	5.64 ± 0.09	5.73 ± 0.08	5.58 ± 0.10	5.52 ± 0.15
4 months	5.19 ± 0.11	5.27 ± 0.06	5.15 ± 0.06	5.14 ± 0.09
Chloride (meq/L)				
2 months	108 ± 0	109 ± 0	108 ± 0	108 ± 1
4 months	110 ± 1	110 ± 1	111 ± 1*	111 ± 1
Calcium (mg/dL)				
2 months	11.0 ± 0.2	10.9 ± 0.2	10.8 ± 0.1	10.6 ± 0.1*
4 months	10.7 ± 0.1	10.4 ± 0.1	10.6 ± 0.0	10.4 ± 0.1
Inorganic phosphorus (mg/dL)				
2 months	6.7 ± 0.2	6.6 ± 0.1	7.1 ± 0.2	7.6 ± 0.3*
4 months	5.3 ± 0.2	4.9 ± 0.2	5.2 ± 0.2	5.3 ± 0.3
Total protein (g/dL)				
2 months	6.9 ± 0.1	7.1 ± 0.1	6.9 ± 0.1	6.8 ± 0.1
4 months	7.8 ± 0.1	7.7 ± 0.1	7.7 ± 0.1	7.3 ± 0.1**
6 months	7.9 ± 0.1	7.8 ± 0.1	7.6 ± 0.1*	7.5 ± 0.1**
Albumin (g/dL)				
2 months	3.79 ± 0.03	3.85 ± 0.03	3.76 ± 0.03	3.64 ± 0.03**
4 months	4.02 ± 0.04	3.98 ± 0.04	3.99 ± 0.03	3.80 ± 0.05**
Albumin/globulin ratio				
2 months	1.22 ± 0.03	1.21 ± 0.02	1.20 ± 0.03	1.17 ± 0.02
4 months	1.06 ± 0.02	1.09 ± 0.03	1.09 ± 0.02	1.10 ± 0.01
Total bilirubin (mg/dL)				
2 months	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
4 months	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0

TABLE G1
Clinical Chemistry Data for Rats in the 6-Month Gavage Studies of Mercuric Chloride (continued)

	Vehicle Control	0.312 mg/kg	1.25 mg/kg	5 mg/kg
Female (continued)				
n	10	10	10	10
Acid phosphatase (IU/L)				
2 months	15 ± 2	12 ± 2	16 ± 3	15 ± 3
4 months	85 ± 4[b]	72 ± 11	54 ± 8*	68 ± 7
6 months	103 ± 14	93 ± 8	65 ± 6*	82 ± 9
Alkaline phosphatase (IU/L)				
2 months	22 ± 8	12 ± 2	20 ± 3[b]	50 ± 20
4 months	163 ± 19[b]	91 ± 12	104 ± 22	677 ± 119*
6 months	206 ± 26	191 ± 20	263 ± 27	1,309 ± 219**
Alanine aminotransferase (IU/L)				
2 months	36 ± 1	35 ± 1	36 ± 2	43 ± 6
4 months	34 ± 1	31 ± 1	32 ± 2	29 ± 1**
6 months	42 ± 2	40 ± 2	36 ± 3*	51 ± 9
Aspartate aminotransferase (IU/L)				
2 months	76 ± 3	76 ± 2	75 ± 3	78 ± 2
4 months	65 ± 3	64 ± 2	60 ± 1	63 ± 1
Lactate dehydrogenase (IU/L)				
2 months	386 ± 40	391 ± 43	392 ± 45	456 ± 42
4 months	404 ± 36	382 ± 29	351 ± 34	384 ± 22
6 months	869 ± 97	971 ± 108	818 ± 93	907 ± 93
Ornithine carbamoyltransferase (IU/L)				
2 months	5 ± 0	4 ± 1[b]	6 ± 1	6 ± 1
4 months	5 ± 1[b]	7 ± 1[b]	10 ± 3[c]	5 ± 1[d]
Sorbitol dehydrogenase (IU/L)				
2 months	10 ± 0	10 ± 0	10 ± 1	11 ± 0
4 months	11 ± 1	10 ± 1	11 ± 1	12 ± 1
6 months	6 ± 1	6 ± 1	6 ± 1[b]	6 ± 0[b]
Serum cholinesterase (IU/L)				
2 months	3,553 ± 114	3,756 ± 172	3,389 ± 138	2,688 ± 130**
4 months	4,732 ± 65	4,390 ± 180	4,340 ± 174	3,571 ± 171**
6 months	4,209 ± 319	4,042 ± 197	3,815 ± 114	3,527 ± 123**
pH				
2 months	7.40 ± 0.27	7.50 ± 0.31	7.20 ± 0.36	8.10 ± 0.23
4 months	6.70 ± 0.30	6.30 ± 0.26	6.50 ± 0.17	6.30 ± 0.21

* 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
[b] n=9
[c] n=7
[d] n=8

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

	Vehicle Control	2.5 mg/kg	5 mg/kg
Male			
n	10	9	10
Clinical chemistry			
Blood urea nitrogen (mg/dL)	13.5 ± 0.4	13.3 ± 0.4	14.3 ± 0.6
Alkaline phosphatase (IU/L)	49 ± 2	47 ± 3	46 ± 2
Alanine aminotransferase (IU/L)	43 ± 4	38 ± 4[b]	39 ± 4
Sorbitol dehydrogenase (IU/L)	7 ± 0	6 ± 0[b]	7 ± 0
Serum cholinesterase (IU/L)	990 ± 42	1,039 ± 35	1,066 ± 33
Urinalysis			
Urine γ-glutamyltransferase (IU/L)	1,678 ± 225	823 ± 61	805 ± 42*
Specific gravity	1.044 ± 0.001	1.042 ± 0.001	1.043 ± 0.001
Urea nitrogen (IU/L)	29 ± 3	22 ± 1	23 ± 2
Urine alkaline phosphatase (IU/L)	134 ± 18	85 ± 7	99 ± 5
Urine aspartate aminotransferase (IU/L)	14 ± 1[c]	15 ± 1**	18 ± 2**
Urine creatinine (IU/L)	3 ± 0	2 ± 0	2 ± 0
Urine lactate dehydrogenase (IU/L)	36 ± 3	26 ± 1	31 ± 2*
Urine volume (mL)	4 ± 1	6 ± 1	6 ± 0
Female			
Clinical chemistry			
n	10	10	10
Blood urea nitrogen (mg/dL)	12.8 ± 0.4	12.6 ± 0.3	13.0 ± 0.6
Alkaline phosphatase (IU/L)	32 ± 1	29 ± 1	32 ± 2
Alanine aminotransferase (IU/L)	29 ± 2	29 ± 1	29 ± 1
Sorbitol dehydrogenase (IU/L)	5 ± 0	5 ± 0	5 ± 0
Serum cholinesterase (IU/L)	3,895 ± 106	4,023 ± 131	3,706 ± 150
Urinalysis			
n	8	9	10
Urine γ-glutamyltransferase (IU/L)	242 ± 25	519 ± 50	310 ± 16**
Specific gravity	1.029 ± 0.004	1.035 ± 0.003	1.020 ± 0.003
Urea nitrogen (IU/L)	15 ± 1	22 ± 1	11 ± 1
Urine alkaline phosphatase (IU/L)	18 ± 2	49 ± 8*	29 ± 3**
Urine aspartate aminotransferase (IU/L)	6 ± 1	11 ± 2	9 ± 2**
Urine creatinine (IU/L)	1 ± 0	1 ± 0	1 ± 0
Urine lactate dehydrogenase (IU/L)	12 ± 1	21 ± 2	10 ± 1
Urine volume (mL)	8 ± 2	5 ± 1	12 ± 2

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=10
[c] n=9

TABLE G3
Clinical Chemistry Data for Mice in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	1.25 mg/kg	5 mg/kg	20 mg/kg
Male				
n	10	10	10	10
Blood urea nitrogen (mg/dL)				
2 months	24.6 ± 1.0[b]	24.3 ± 2.3[b]	24.7 ± 1.0[c]	20.8 ± 1.0[d]
4 months	19.5 ± 1.2[b]	19.8 ± 0.7[b]	18.9 ± 0.9[d]	17.1 ± 0.9[b]
Calcium (mg/dL)				
4 months	10.9 ± 0.1[e]	10.5 ± 0.2[f]	10.7 ± 0.3[g]	10.3 ± 0.2[h]
Total protein (g/dL)				
2 months	7.8 ± 0.3[i]	8.0 ± 0.3[i]	7.6 ± 0.4[h]	7.4 ± 0.2[g]
4 months	6.8 ± 0.1[f]	6.8 ± 0.1[c]	6.6 ± 0.1[c]	6.4 ± 0.1*[i]
Albumin (g/dL)				
2 months	3.78 ± 0.10[d]	3.70 ± 0.04	3.75 ± 0.09[f]	3.65 ± 0.03[f]
4 months	3.58 ± 0.06[d]	3.51 ± 0.04[d]	3.47 ± 0.05[c]	3.41 ± 0.05[d]
Albumin/globulin ratio				
2 months	0.94 ± 0.02[i]	0.90 ± 0.06[i]	0.93 ± 0.03[h]	1.00 ± 0.07[g]
4 months	1.08 ± 0.04[f]	1.11 ± 0.03[c]	1.10 ± 0.03[c]	1.20 ± 0.06[i]
Acid phosphatase (IU/L)				
2 months	4 ± 1[d]	6 ± 2[d]	4 ± 1[c]	1 ± 0*[d]
4 months	44 ± 10[b]	55 ± 10	44 ± 12	38 ± 8
6 months	29 ± 3	29 ± 5[c]	23 ± 3[d]	19 ± 3*[b]
Alkaline phosphatase (IU/L)				
2 months	2 ± 1[d]	5 ± 2[d]	9 ± 4[c]	1 ± 0[d]
4 months	31 ± 11[b]	33 ± 15	32 ± 9	30 ± 12[b]
6 months	32 ± 4	36 ± 8[c]	88 ± 33[b]	59 ± 15[b]
Alanine aminotransferase (IU/L)				
2 months	236 ± 31	195 ± 24	177 ± 36[b]	197 ± 31[b]
4 months	101 ± 18	99 ± 17	105 ± 17	92 ± 19
Lactate dehydrogenase (IU/L)				
2 months	1,060 ± 113	1,155 ± 95	1,022 ± 101[b]	991 ± 97[b]
4 months	567 ± 49	576 ± 64[b]	619 ± 107	513 ± 45
Sorbitol dehydrogenase (IU/L)				
2 months	93 ± 9	98 ± 7	99 ± 7	91 ± 8
4 months	81 ± 7[d]	82 ± 7[d]	90 ± 12[d]	71 ± 5[d]
pH				
2 months	6.30 ± 0.21	6.44 ± 0.24[b]	6.50 ± 0.17	6.20 ± 0.20
4 months	5.60 ± 0.16	5.50 ± 0.22	5.30 ± 0.15	5.40 ± 0.22

TABLE G3
Clinical Chemistry Data for Mice in the 6-Month Gavage Studies of Mercuric Chloride (continued)

	Vehicle Control	1.25 mg/kg	5 mg/kg	20 mg/kg
Female				
n	10	10	10	10
Blood urea nitrogen (mg/dL)				
2 months	25.7 ± 1.0[f]	23.1 ± 1.2	20.3 ± 1.0**[b]	19.8 ± 1.4**[c]
4 months	18.4 ± 0.9[b]	17.7 ± 1.2[d]	15.8 ± 1.5[d]	15.4 ± 0.8[c]
Total protein (g/dL)				
4 months	6.7 ± 0.1[h]	6.8 ± 0.1[f]	6.2 ± 0.1*[i]	5.8 ± 0.1*[h]
Albumin (g/dL)				
2 months	3.70 ± 0.40[e]	3.78 ± 0.09[f]	3.90 ± 0.07[c]	3.68 ± 0.07[i]
4 months	3.92 ± 0.03[f]	3.84 ± 0.05[c]	3.61 ± 0.05**[c]	3.33 ± 0.03**[h]
Albumin/globulin ratio				
4 months	1.37 ± 0.07[h]	1.33 ± 0.02[f]	1.36 ± 0.05[i]	1.37 ± 0.03[h]
Acid phosphatase (IU/L)				
2 months	1 ± 0[g]	1 ± 0[c]	1 ± 0[c]	1 ± 0[c]
4 months	32 ± 10[d]	22 ± 4[b]	30 ± 3[b]	19 ± 5[c]
6 months	13 ± 4[b]	8 ± 2[f]	17 ± 6[c]	15 ± 3[c]
Alkaline phosphatase (IU/L)				
2 months	1 ± 0[g]	2 ± 1[c]	1 ± 0[c]	0 ± 0[f]
4 months	21 ± 8[c]	20 ± 6[b]	34 ± 12[b]	31 ± 20[c]
6 months	45 ± 11[b]	32 ± 20[f]	41 ± 16[f]	54 ± 22[c]
Alanine aminotransferase (IU/L)				
2 months	150 ± 18[b]	135 ± 23	129 ± 18	139 ± 30
4 months	76 ± 18	87 ± 24	74 ± 15	90 ± 16
Lactate dehydrogenase (IU/L)				
2 months	1,081 ± 87[d]	920 ± 92	887 ± 87[b]	848 ± 112[d]
4 months	494 ± 56	499 ± 61	419 ± 46	461 ± 79[d]
Sorbitol dehydrogenase (IU/L)				
2 months	81 ± 8	81 ± 8	73 ± 6	79 ± 6
4 months	64 ± 4[d]	62 ± 5[d]	56 ± 3[c]	63 ± 7[c]
pH				
2 months	5.75 ± 0.25[d]	6.38 ± 0.18[d]	5.75 ± 0.31[d]	5.88 ± 0.23[d]
4 months	5.22 ± 0.15[b]	5.33 ± 0.17[b]	5.33 ± 0.17[b]	5.00 ± 0.00[c]

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=9
[c] n=7
[d] n=8
[e] n=2
[f] n=6
[g] n=4
[h] n=3
[i] n=5

TABLE G4
Clinical Chemistry and Urinalysis Data for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	5 mg/kg	10 mg/kg
Male			
Clinical chemistry			
n	10	10	10
Blood urea nitrogen (mg/dL)	18.6 ± 1.0[b]	19.2 ± 0.7[c]	20.4 ± 2.1[c]
Alkaline phosphatase (IU/L)	36 ± 2	39 ± 1	39 ± 1
Alanine aminotransferase (IU/L)	61 ± 13[c]	46 ± 4	49 ± 8
Sorbitol dehydrogenase (IU/L)	37 ± 2	39 ± 2[c]	36 ± 3
Serum cholinesterase (IU/L)	9,125 ± 667[c]	9,777 ± 375	8,911 ± 276
Urinalysis			
n	6	8	5
Urine γ-glutamyltransferase (IU/L)	130 ± 48	79 ± 10	99 ± 30
Specific gravity	1.021 ± 0.007[d]	1.018 ± 0.003	1.024 ± 0.007
Urea nitrogen (IU/L)	1 ± 0	1 ± 0	1 ± 0
Urine alkaline phosphatase (IU/L)	8 ± 2	13 ± 2*	13 ± 4
Urine aspartate aminotransferase (IU/L)	5 ± 1	4 ± 1	4 ± 1
Urine creatinine (IU/L)	0 ± 0	0 ± 0	0 ± 0
Urine lactate dehydrogenase (IU/L)	2 ± 1	2 ± 1	3 ± 2
Urine volume (mL)	4 ± 2	5 ± 1	3 ± 1
Female			
Clinical chemistry			
n	10	10	10
Blood urea nitrogen (mg/dL)	16.2 ± 0.8	12.9 ± 0.5**	12.7 ± 0.4**
Alkaline phosphatase (IU/L)	77 ± 4	71 ± 4	69 ± 4
Alanine aminotransferase (IU/L)	62 ± 8	41 ± 3*	51 ± 8
Sorbitol dehydrogenase (IU/L)	25 ± 2	26 ± 1	28 ± 2
Serum cholinesterase (IU/L)	11,711 ± 506	11,033 ± 365	11,545 ± 601
Urinalysis			
n	5	6	5
Urine γ-glutamyltransferase (IU/L)	93 ± 27	260 ± 38	360 ± 60
Specific gravity	1.020 ± 0.006[e]	1.020 ± 0.002[d]	1.020 ± 0.010[f]
Urea nitrogen (IU/L)	1 ± 0	1.3 ± 0.2	1.0 ± 0.3
Urine alkaline phosphatase (IU/L)	15 ± 4	29 ± 4	31 ± 4
Urine aspartate aminotransferase (IU/L)	5 ± 2	9 ± 3	7 ± 3[g]
Urine creatinine (IU/L)	0 ± 0	0 ± 0	0 ± 0
Urine lactate dehydrogenase (IU/L)	2 ± 1	6 ± 2	5 ± 2
Urine volume (mL)	2 ± 1	1 ± 0	1 ± 0

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=8
[c] n=9
[d] n=5
[e] n=4
[f] n=2
[g] n=6

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF MERCURIC CHLORIDE

Mercuric chloride was obtained from the Fisher Scientific Company (Fairlawn, NJ) in one lot (lot number 792985), which was used throughout the studies. The purity and elemental analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports performed in support of the mercuric chloride studies are on file at the National Institutes of Environmental Health Sciences (NIEHS).

The study chemical, a white powder, was identified as mercuric chloride by elemental analyses. The analyses were performed at two independent analytical laboratories: Galbraith Laboratories, Incorporated (Knoxville, TN), and Huffman Laboratories, Incorporated (Wheat Ridge, CO).

The purity was determined by elemental analyses, X-ray emission analysis, and ultraviolet/visible and nuclear magnetic resonance (NMR) spectroscopies. For X-ray emission analysis the compound was analyzed using filtered copper radiation with a platinum target. Because mercuric chloride reacts with Karl Fischer reagent, water content was determined using NMR quantitation with deuterated methanol and maleic acid as an internal standard.

Elemental analyses determined that the mercury content ranged between 99.4% and 99.9% and chloride content ranged between 98.0% and 100.3% of the theoretical values for mercuric chloride. Water content was found to be less than 0.1% by NMR quantitation. Ne detectable trace inorganic impurities with an atomic number greater than 19 were found using X-ray emission analysis. Ultraviolet/visible and NMR spectroscopies detected no organic impurities. The NMR spectra showed only the internal standard, tetramethylsilane, the solvent, methanol, and water (Figure H1). All spectra were consistent with the structure of mercuric chloride (*Sadtler Standard Spectra*). The overall data supported a purity of greater than 99%.

Because of the physical and chemical properties of mercuric chloride, no bulk chemical stability studies were performed. Mercuric chloride has a melting point of 277° C (*Merck Index*, 1976). The study chemical was determined to have a melting point between 280.7° C and 282.3° C. Because the compound is somewhat volatile under normal room conditions, the bulk chemical was stored protected from light at room temperature in a Nalgene® container.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations for the studies were prepared by mixing the appropriate amount of mercuric chloride in deionized water (Table H1). Dose formulations were stored protected from light and at room temperature for up to 3 weeks. For the 16-day studies, dose formulations were prepared at study initiation only, except for the 1.25 ppm dose group in rats, which was also prepared at week 2. For the 6-month and 2-year studies, dose formulations were prepared at least every 3 weeks.

Stability studies were not conducted because no appropriate analytical procedures were available to differentiate between the covalently bonded and ionic species of mercuric chloride. However, the study laboratory did repeat analyses over a 3-week period and confirmed that the concentrations did not change.

Periodic analyses of the dose formulations of mercuric chloride were conducted at the study laboratory and at the analytical chemistry laboratory. Dose concentrations were determined by absorbance at 230 nm using ultraviolet spectrometry against a standard curve. In the 16-day studies, dose formulations

were analyzed at study initiation (Table H2). In the 6-month studies, dose formulations were analyzed prior to initiation, at mid-point, and at the end of the study (Table H3). All dose formulations for rats and mice were within 10% of target concentrations. In the 2-year studies, dose formulations from the dose preparation room were analyzed at least every 8 weeks and from the animal room every 5 to 6 months (Tables H4 and H5). All dose formulations analyzed by the study laboratory were within 10% of target concentrations. Dose formulations were sampled in triplicate for periodic referee analyses by the analytical chemistry laboratory and compared to the study laboratory results. Results from both laboratories were in good agreement (Table H6). Reports of analyses performed in support of these studies are on file at NIEHS.

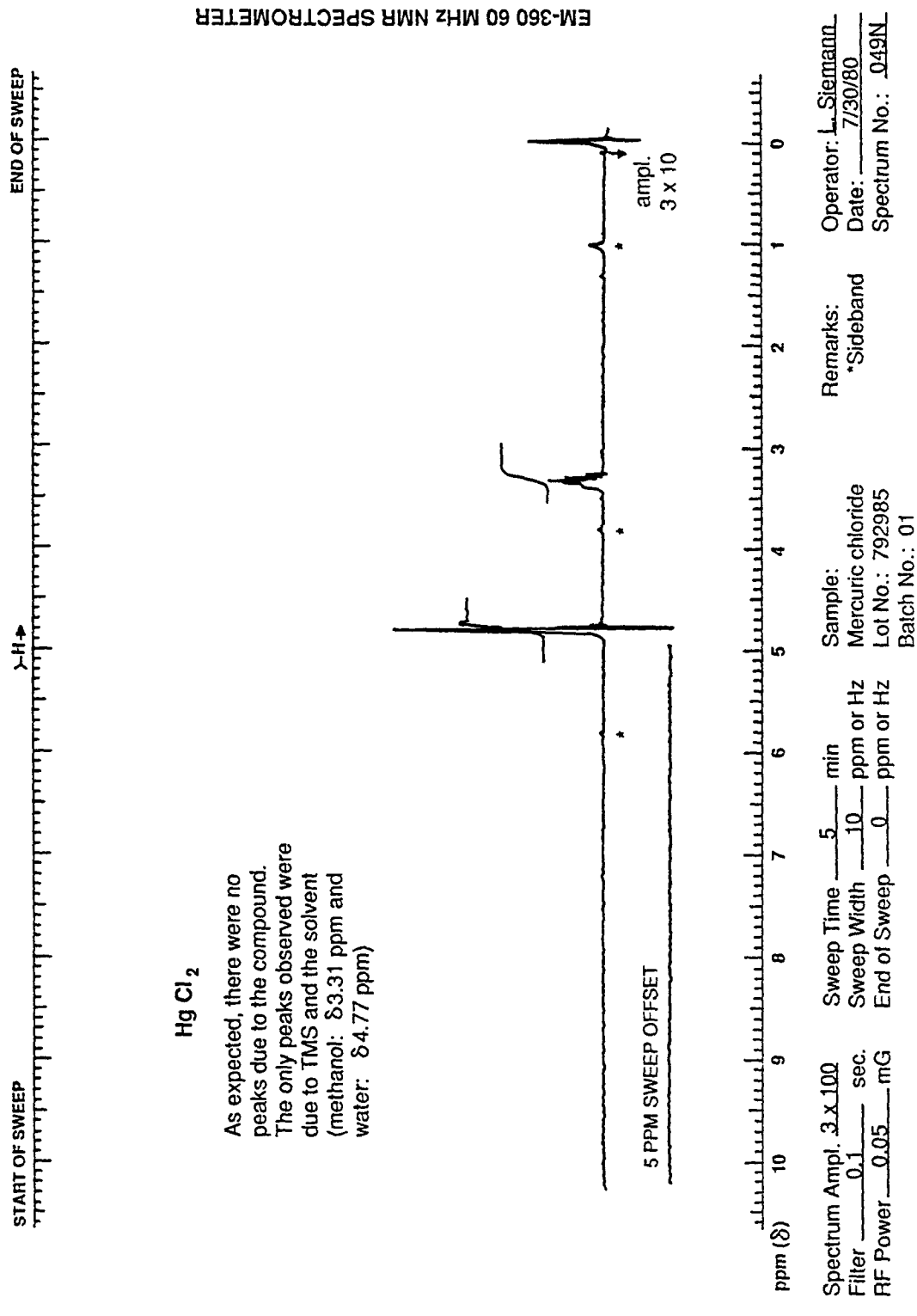

FIGURE H1
Nuclear Magnetic Resonance Spectrum of Mercuric Chloride

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of Mercuric Chloride

16-Day Studies	6-Month Studies	2-Year Studies
Preparation		
Mercuric chloride was dissolved in the appropriate amount of deionized water. Dose formulations were prepared once, except for the 1.25 ppm rat dose, which was prepared twice.	Same as 16-day studies, except dose formulations were prepared fresh every 3 weeks.	Same as 6-month studies
Concentration		
Rats: 0, 0.125, 0.250, 0.500, 1.0, and 2.0 mg/mL Mice: 0, 0.50, 1.00, 2.00, 4.00, and 8.00 mg/mL	Rats: 0, 0.0625, 0.125, 0.25, and 0.5 mg/mL Mice: 0, 0.125, 0.25, 0.5, 1.0, and 2.0 mg/mL	0, 0.5, and 1.0 mg/mL
Chemical Lot Number		
792985	Same as 16-day studies	Same as 16-day studies
Maximum Storage Time		
2 weeks	Same as 6-month studies	Same as 6-month studies
Storage Conditions		
Protected from light at room temperature in Nalgene® container	Same as 16-day studies	Same as 16-day studies

TABLE H2
Results of Analysis of Dose Formulations for Rats and Mice in the 16-Day Gavage Studies of Mercuric Chloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
Rats				
23 March 1981	24 March 1981	0	0	–
		0.125	0.102	–18[c]
		0.250	0.255	+2
		0.50	0.483	–3
		1.00	1.03	+3
		2.00	2.02	+1
Mice				
24 March 1981	25 March 1981	0.50	0.50	+1
		1.00	1.05	+5
		2.00	2.03	+2
		4.00	4.10	+3
		8.00	8.13	+2

[a] Target concentrations for rats: 0.125 mg/mL = 1.25 mg/kg; 0.250 mg/mL = 2.5 mg/kg; 0.50 mg/mL = 5 mg/kg; 1.00 mg/mL = 10 mg/kg; 2.00 mg/mL = 20 mg/kg. Target concentrations for mice: 0.50 mg/mL = 5 mg/kg; 1.00 mg/mL = 10 mg/kg; 2.00 mg/mL = 20 mg/kg; 4.00 mg/mL = 40 mg/kg; and 8.00 mg/mL = 80 mg/kg. Dosing volume = 10 mL/kg.

[b] Results of duplicate analyses

[c] The low average result was confirmed by additional analyses. A fresh batch of the dose formulation was prepared and analyzed on 30 March 1981 and found to contain 100% of the target concentration. This preparation was substituted for the 23 March 1981 preparation on 30 March 1981 and used until study termination.

TABLE H3
Results of Analysis of Dose Formulations for Rats and Mice in the 6-Month Gavage Studies of Mercuric Chloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
Rats				
28 September 1981	28 September 1981	0.0624	0.0630	+1
		0.125	0.127	+2
		0.250	0.255	+2
		0.500	0.512	+2
		1.00	1.02	+2
21 December 1981	23 December 1981	0.0624	0.655	+5
		0.125	0.121	–3
		0.250	0.248	–1
		0.500	0.482	–4
		1.00	0.978	–2
11 March 1982	12 March 1982	0.0625	0.0579	–7
		0.125	0.116	–7
		0.250	0.226	–10
		0.500	0.460	–8
		1.00	0.924	–8
19 October 1981	20 October 1981	0.500	0.485	–3
Mice				
28 September 1981	29 September 1981	0.125	0.138	+10
		0.250	0.252	+1
		0.500	0.515	+3
		1.00	1.01	+1
		2.00	1.98	–1
21 December 1981	23 December 1981	0.125	0.127	+2
		0.250	0.246	–2
		0.500	0.507	+1
		1.00	0.987	–1
		2.00	1.96	–2
11 March 1982	12 March 1982	0.125	0.126	+1
		0.250	0.252	+2
		0.500	0.490	–2
		1.00	0.975	–2
		2.00	1.94	–3
19 October 1981	20 October 1981	0.500	0.485	–3

[a] Target concentrations for rats: 0.0624 mg/mL = 0.312 mg/kg; 0.125 mg/mL = 0.625 mg/kg; 0.250 mg/mL = 1.25 mg/kg; 0.500 mg/mL = 2.5 mg/kg; 1.00 mg/mL = 5.0 mg/kg. Target concentrations for mice: 0.125 mg/mL = 0.625 mg/kg; 0.250 mg/mL = 1.25 mg/kg; 0.500 mg/mL = 2.5 mg/kg; 1.00 mg/mL = 5.0 mg/kg; and 2.00 mg/mL = 10 mg/kg. Dosing volume = 5 mL/kg.

[b] Results of duplicate analyses

TABLE H4
Results of Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Mercuric Chloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
24 February 1983	28 February 1983	0.5	0.514	+3
		1.0	1.02	+2
	7 March 1983	0.5	0.507[c]	+1
		1.0	1.01	+1
28 April 1983	29 April 1983	0.5	0.494	–1
		1.0	0.98	–2
30 June 1983	7 July 1983	0.5	0.496	–1
		1.0	1.00	0
11 August 1983	22 August 1983	0.5	0.507	+1
		1.0	0.99	–1
1 September 1983	6 September 1983	0.5	0.507	+1
		1.0	1.01	+1
6 October 1983	7 October 1983	0.5	0.490	–2
		1.0	1.00	0
17 November 1983	22 November 1983	0.5	0.516	+3
		1.0	1.01	+1
12 January 1984	17 January 1984	0.5	0.493	–1
		1.0	1.00	0
	1 February 1984	0.5	0.500[c]	0
		1.0	1.01	+1
8 March 1984	13 March 1984	0.5	0.496	–1
		1.0	1.02	+2
3 May 1984	3 May 1984	0.5	0.501	0
		1.0	0.99	–1
28 June 1984	28 June 1984	0.5	0.495	–1
		1.0	1.00	0
	13 July 1984	0.5	0.497[c]	–1
		1.0	1.00	0
28 June 1984	19 July 1984	0.5	0.507	+1
23 August 1984	28 August 1984	0.5	0.509	+2
		1.0	1.02	+2
18 October 1984	22 October 1984	0.5	0.502	0
		1.0	1.01	+1
13 December 1984	13 December 1984	0.5	0.496	–1
		1.0	0.99	–1
	31 December 1984	0.5	0.499[c]	0
		1.0	1.00	0
7 February 1985	7 February 1985	0.5	0.506	+1
		1.0	1.01	+1

TABLE H4
Results of Analysis of Dose Formulations for Rats in the 2-Year Gavage Studies of Mercuric Chloride
(continued)

[a] Target concentrations: 0.500 mg/mL = 2.5 mg/kg; 1.00 mg/mL = 5.0 mg/kg. Dosing volume = 5 mL/kg.
[b] Results of duplicate analyses
[c] Animal room sample

TABLE H5
Results of Analysis of Dose Formulations for Mice in the 2-Year Gavage Studies of Mercuric Chloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
2 March 1983	3 March 1983	0.5	0.494	−1
		1.0	1.00	0
	14 March 1983	0.5	0.496[c]	−1
		1.0	0.99	−1
4 May 1983	4 May 1983	0.5	0.502	0
		1.0	1.01	+1
6 July 1983	7 July 1983	0.5	0.497	−1
		1.0	1.00	0
17 August 1983	22 August 1983	0.5	0.515	+3
		1.0	1.04	+4
7 September 1983	8 September 1983	0.5	0.496	−1
		1.0	1.00	0
12 October 1983	13 October 1983	0.5	0.499	0
		1.0	1.01	+1
23 November 1983	23 November 1983	0.5	0.500	0
		1.0	1.02	+2
18 January 1984	18 January 1984	0.5	0.498	0
		1.0	1.00	0
	6 February 1984	0.5	0.507[c]	+1
		1.0	0.99	−1
14 March 1984	14 March 1984	0.5	0.503	+1
		1.0	1.01	+1
9 May 1984	9 May 1984	0.5	0.495	−1
		1.0	0.98	−2
5 July 1984	5 July 1984	0.5	0.508	+2
		1.0	1.04	+4
	19 July 1984	0.5	0.500[c]	0
		1.0	1.00	0
29 August 1984	29 August 1984	0.5	0.502	0
		1.0	1.02	+2
24 October 1984	24 October 1984	0.5	0.504	+1
		1.0	1.01	+1
	15 November 1984	0.5	0.509[c]	+2
19 December 1984[c]	4 January 1985	0.5	0.503	+1
		1.0	1.02	+2
13 February 1985	13 February 1985	0.5	0.497	−1
		1.0	1.00	0

[a] Target concentrations: 0.500 mg/mL = 2.5 mg/kg; 1.00 mg/mL = 5.0 mg/kg. Dosing volume = 5 mL/kg.
[b] Results of duplicate analyses
[c] Animal room sample

TABLE H6
Results of Referee Analysis of Dose Formulations for Rats and Mice in the 2-Year Gavage Studies of Mercuric Chloride

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
Rats			
24 February 1983	0.5	0.514	0.487 ± 0.004
8 March 1984	1.0	1.02	1.00 ± 0.01
Mice			
7 September 1983	1.0	1.00	1.03 ± 0.03
24 October 1984	0.5	0.504	0.507 ± 0.001

[a] Results of duplicate analyses
[b] Results of triplicate analyses; mean ± standard deviation

APPENDIX I
TISSUE MERCURY CONCENTRATION ANALYSIS

TISSUE MERCURY CONCENTRATION ANALYSIS

PREPARATION AND ANALYSIS OF TISSUE CONCENTRATIONS OF MERCURY

Tissue samples from the kidney, liver, and brain of male and female rats and mice were frozen in liquid nitrogen and stored at −60° C until analyzed by the study laboratory. In the 16-day studies, tissues from the vehicle control and high-dose groups were analyzed for mercury concentrations (Tables I1 and I3). In the 6-month studies, kidney and liver tissues from rats receiving 0, 0.312, 1.25, and 5.0 mg mercuric chloride/kg body weight and from mice receiving 0, 1.25, 5, and 20 mg/kg were analyzed after 2, 4, and 6 months of chemical exposure. Brain tissues analyzed in the 6-month studies were taken from the control and high-dose groups (Tables I2 and I4). Reports of analyses performed in support of the studies are on file at the National Institutes of Environmental Health Sciences.

Analyses of mercury concentrations were performed as described by Fawkes *et al.* (1976). Mercuric chloride standards were prepared in 1% nitric acid. Tissues were weighed, homogenized in deionized water to yield a tissue concentration of 0.1 g/mL, and digested in a mixture of sulfuric acid and nitric acid (2:1) with 5% aqueous potassium permanganate for 72 hours. The solution was decolorized with 12% (w/v) hydroxylamine hydrochloride before diluting to volume with deionized water.

Mercury concentrations in the digested tissues were determined by the cold vapor technique using a Varian 875 AA spectrophotometer with a Varian Model 65 Mercury Vapor Generator Accessory. The digested tissue sample was allowed to react with 20% (w/v) stannous chloride in concentrated hydrochloric acid for 90 seconds before mercury was discharged into the cell. Mercury was detected at 253.7 nm with a slit width of 0.5 mm; the mercury vapor lamp was operated at 3.5 μA. A standard curve was developed using linear regression.

The method of analysis was validated in the 16-day studies using kidney tissues spiked with mercury concentrations ranging from approximately 0.1 to 50 ppm and with liver and brain tissues spiked with concentrations ranging from 0.1 to 10 ppm. Average mercury recoveries were 97% ± 1.3% for kidney, 88% ± 5.4% for liver, and 93% ± 4.3% for brain.

TABLE I1
Tissue Concentrations of Mercury in Rats in the 16-Day Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	20 mg/kg
Male		
n	5	3
Kidney	<1	45.5 ± 11.7
Liver	0.199 ± 0.047	5.69 ± 1.21[b]
Brain	0.172 ± 0.037	0.374 ± 0.270
Female		
n	5	4
Kidney	<1	43.4 ± 16.4
Liver	0.095 ± 0.047	4.41 ± 1.30[b]
Brain	0.172 ± 0.035	0.481 ± 0.154

[a] Mean mercury concentrations are given as ppm ± standard deviation.
[b] n=5

TABLE I2
Tissue Concentrations of Mercury in Rats in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	0.312 mg/kg	1.25 mg/kg	5 mg/kg
Male				
Kidney				
2 months	1.05 ± 0.90	24.0 ± 1.20	61.1 ± 13.4	94.6 ± 39.5
4 months	0.83 ± 0.41	34.5 ± 4.67	65.6 ± 5.82	86.8 ± 8.75
6 months	0.10 ± 0.01	47.9 ± 14.7	89.6 ± 14.6	92.2 ± 4.57
Liver				
2 months	0.19 ± 0.11	<0.31	0.36 ± 0.06	1.03 ± 0.44
4 months	0.17 ± 0.04	<0.11	0.46 ± 0.14	1.83 ± 0.72
6 months	0.15 ± 0.04	<0.11	0.56 ± 0.12	1.85 ± 0.26
Brain				
2 months	0.02 ± 0.03	–[b]	–	0.07 ± 0.02
4 months	0.03 ± <0.01	–	–	0.01 ± <0.01
6 months	0.03 ± 0.01	–	–	0.04 ± 0.01
Female				
Kidney				
2 months	1.13 ± 0.89	30.5 ± 4.29	102 ± 21.2	103 ± 24.5
4 months	0.81 ± 0.39	56.4 ± 8.39	98.0 ± 8.06	123 ± 9.87
6 months	0.12 ± 0.03	47.1 ± 14.5	86.2 ± 13.6	92.9 ± 7.29
Liver				
2 months	0.20 ± 0.08	<0.23	0.25 ± 0.04	1.20 ± 0.50
4 months	0.17 ± 0.05	<0.14	0.55 ± 0.51	1.79 ± 0.27
6 months	0.11 ± 0.03	0.14 ± 0.04	0.55 ± 0.07	1.97 ± 0.26
Brain				
2 months	0.02 ± 0.02	–	–	0.08 ± 0.04
4 months	0.03 ± 0.01	–	–	<0.03
6 months	0.05 ± 0.02	–	–	<0.06

[a] Mean mercury concentrations are given as ppm ± standard deviation; ten animals per group.
[b] Mercury levels in brain tissues were measured in the vehicle control and high-dose groups only.

TABLE I3
Tissue Concentrations of Mercury in Mice in the 16-Day Gavage Studies of Mercuric Chloride[a]

	Vehicle Control[b]	40 mg/kg	
		Male	Female
n	10	4	5
Kidney	0.408 ± 0.158	171.3 ± 47.7	116.0 ± 8.7
Liver	0.300 ± 0.054	34.65 ± 21.57	29.48 ± 10.05
Brain	0.421 ± 0.08	0.891 ± 0.376	0.914 ± 0.224

[a] Mean mercury concentrations are given as ppm ± standard deviation.
[b] Pooled data for male and female mice

TABLE I4
Tissue Concentrations of Mercury in Mice in the 6-Month Gavage Studies of Mercuric Chloride[a]

	Vehicle Control	1.25 mg/kg	5 mg/kg	20 mg/kg
Male				
Kidney				
2 months	0.27 ± 0.21	7.25 ± 2.08	36.7 ± 10.5	112 ± 12.9
4 months	0.27 ± 0.03	7.29 ± 1.60	26.7 ± 7.75	105 ± 10.1
6 months	0.42 ± 0.13	7.39 ± 2.01	36.1 ± 6.84	87.3 ± 9.83
Liver				
2 months	0.07 ± 0.02	1.27 ± 1.22	2.73 ± 0.46	9.95 ± 1.81
4 months	0.02 ± 0.04	0.95 ± 0.25	9.73 ± 3.52	9.73 ± 3.52
6 months	0.05 ± 0.03	0.85 ± 0.09	2.98 ± 0.84	10.6 ± 3.94
Brain				
2 months	0.12 ± 0.03	–[b]	–	0.36 ± 0.06
4 months	0.19 ± 0.05	–	–	0.54 ± 0.11
6 months	0.40 ± 0.14	–	–	0.59 ± 0.10
Female				
Kidney				
2 months	0.36 ± 0.57	7.65 ± 0.93	27.0 ± 4.77	88.3 ± 18.2
4 months	0.21 ± 0.09	8.53 ± 0.86	23.7 ± 7.51	97.4 ± 14.4
6 months	0.44 ± 0.28	10.3 ± 1.78	40.6 ± 7.75	88.4 ± 9.68
Liver				
2 months	0.09 ± 0.03	1.02 ± 0.54	2.83 ± 0.55	8.79 ± 1.67
4 months	0.04 ± 0.05	0.88 ± 0.55	3.86 ± 0.82	13.5 ± 4.00
6 months	0.08 ± 0.03	1.12 ± 0.25	3.38 ± 0.31	13.4 ± 2.73
Brain				
2 months	0.15 ± 0.08	–	–	0.45 ± 0.15
4 months	0.19 ± 0.03	–	–	0.68 ± 0.14
6 months	0.28 ± 0.09	–	–	1.09 ± 0.21

[a] Mean mercury concentrations are given as ppm ± standard deviation; ten animals per group.
[b] Mercury levels in brain tissues were measured in the vehicle control and high-dose groups only.

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

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE J2
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.70 ± 0.90	21.1–24.9	24
Crude fat (% by weight)	5.35 ± 0.77	3.3–6.5	24
Crude fiber (% by weight)	3.46 ± 0.28	2.8–3.8	24
Ash (% by weight)	6.68 ± 0.32	6.2–7.3	24
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalanine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.098	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	12,267 ± 4,841	4,100–24,000	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α–Tocopherol (ppm)	37.95 ± 9.41	22.5–48.9	8
Thiamine (ppm)	19.17 ± 3.75	12.0–27.0	24
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.37	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 2.70	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 20.59	10.6–65.0	8
Choline (ppm)	3,089 ± 308	2,400–3,430	8
Minerals			
Calcium (%)	1.26 ± 0.14	0.95–1.54	24
Phosphorus (%)	0.96 ± 0.06	0.87–1.10	24
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	360.54 ± 100	255.0–523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.34	1.04–2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.57 ± 0.17	0.17–0.94	24
Cadmium (ppm)	<0.10	–	24
Lead (ppm)	0.62 ± 0.26	0.33–1.32	24
Mercury (ppm)	<0.05	–	24
Selenium (ppm)	0.33 ± 0.06	0.21–0.42	24
Aflatoxins (ppb)	<5.0	–	24
Nitrate nitrogen (ppm)	10.19 ± 5.20	<0.10–22.0	24
Nitrite nitrogen (ppm)	0.92 ± 1.66	<0.10–7.20	24
BHA (ppm)[b]	2.13 ± 0.61	<2.00–5.00	24
BHT (ppm)[b]	2.17 ± 1.17	<1.00–4.00	24
Aerobic plate count (CFU/g)[c]	51,595 ± 41,719	7,700–130,000	24
Coliform (MPN/g)[d]	44.46 ± 120	3.00–460	24
E. coli (MPN/g)[e]	3.04 ± 0.20	3.00–4.0	24
Total nitrosamines (ppb)[f]	6.32 ± 6.14	1.80–30.90	24
N-Nitrosodimethylamine (ppb)[f]	5.30 ± 6.17	0.80–30.00	24
N-Nitrosopyrrolidine (ppb)[f]	1.02 ± 0.02	0.90–1.70	24
Pesticides (ppm)			
α-BHC[g]	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.1		24
Estimated PCBs	<0.2		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.1		24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion[h]	0.12 ± 0.10	0.05–0.45	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

TABLE J4
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] One lot milled 17 October 1984 had a value of 4.0 MPN.
[f] All values were corrected for percent recovery.
[g] BHC = hexachlorocyclohexane or benzene hexachloride
[h] Thirteen lots contained more than 0.05 ppm.

APPENDIX K
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 using blood samples drawn from extra (sentinel) animals in the study rooms. These animals are untreated, and are subjected together with the study animals 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.

Rats

For the 6-month studies, samples for viral screening were collected from the orbital sinuses of five male and five female sentinel rats. The blood was allowed to clot, the sera were separated and processed appropriately, and the samples were sent to Microbiological Associated, Incorporated (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
PVM (pneumonia virus of mice)	Study termination
Sendai	Study termination
	Study termination
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
RCV (rat coronavirus)	Study termination

For the 2-year studies, samples for viral screening were collected from the orbital sinuses of five male and five female sentinel rats at 6, 12, and 18 months into the studies. At the end of the study, five male and five female control rats were bled from the orbital sinus to provide samples for viral antibody titers. The blood was allowed to clot, the sera were separated and processed appropriately, and the samples were sent to Microbiological Associated, Incorporated (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
H-1	6, 12, 18, and 24 months
KRV	6, 12, 18, and 24 months
PVM	6, 12, and 18 months
Sendai	6, 12, and 18 months
ELISA	
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
PVM	24 months
Sendai	24 months
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, 18, and 24 months

Mice

For the 6-month studies, samples for viral screening were collected from the orbital sinus of five male and five female sentinel mice. The blood was allowed to clot, the sera were separated and processed appropriately, and the samples were sent to Microbiological Associated, Incorporated (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Complement Fixation	
LCM	Study termination
MHV (mouse hepatitis virus)	Study termination

For the 2-year studies, samples for viral screening were collected from the orbital sinuses of five male and five female sentinel mice at 6, 9, and 12 months into the studies. Samples were also taken from five sentinel females at 21 months, but mortality reduced the number of sentinel males available to three. At the end of the study, five male and five female control mice were bled from the orbital sinus to provide samples for viral antibody titers. The blood was allowed to clot, the sera were separated and processed appropriately, and the samples were sent to Microbiological Associated, Incorporated (Bethesda, MD), for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
Ectromelia virus	6, 9, and 12 months
GDVII	6, 9, and 12 months
K (papovirus)	25 months
MVM	6, 9, 12, 21, and 25 months
Polyoma virus	6, 9, 12, 21, and 25 months
PVM	6, 9, and 12 months
Reovirus 3	6, 9, and 12 months
Sendai	6, 9, and 12 months
Complement Fixation	
LCM	6, 9, 12, 21, and 25 months
Mouse adenoma virus	6, 9, and 12 months

Method of Analysis (continued)	Time of Analysis (continued)
ELISA	
Ectromelia virus	21 and 25 months
GDVII	21 and 25 months
Mouse adenoma virus	21 and 25 months
M. arthritidis	21 and 25 months
M. pulmonis	21 and 25 months
MHV	6, 9, 12, 21, and 25 months
PVM	21 and 25 months
Sendai	21 and 25 months
Reovirus 3	21 and 25 months
Immunofluorescent antibody	
EDIM (epipzootic diarrhea of infant mice)	21 and 25 months

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 6-Month and 2-Year Gavage Studies of Mercuric Chloride

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
6-Month Studies			
Rats			
	6 months	0/10	None
Mice			
	6 months	0/10	None
2-Year Studies			
Rats			
	6 months	4/10	PVM
	12 months	10/10	PVM
	18 months	10/10	PVM
	24 months	10/10	PVM
		2/10	KRV
		1/10	possible *M. arthritidis*
Mice			
	6 months	7/10	MHV
	9 months	8/10	MHV
	12 months	3/9	MHV
		1/9	PVM
	21 months	8/8	EDIM
		2/8	PVM
		1/8	MHV
	5 months	10/10	PVM
		7/10	EDIM
		4/10	MHV

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF FEBRUARY 1993

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	Trichlorethylene (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	Telone II® (1,3-Dichloropropene)
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) phosponium 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 Pariffins (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

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF FEBRUARY 1993 (CONT.)

TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
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	α-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
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
394	Acetaminophen
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
409	Quercetin
410	Naphthalene
411	C.I. Pigment Red 23
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
415	Polysorbate 80
419	HC Hellow 4

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709.

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

SPECIAL FOURTH-CLASS RATE
POSTAGE AND FEES PAID
DHHS/NIH
Permit No. G-763

Official Business
Penalty for Private Use - $300

NIH Publication No. 93-3139
February 1993