NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

MANGANESE (II) SULFATE MONOHYDRATE

(CAS NO. 10034-96-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NTP TR 428

NIH Publication No. 94-3159

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

FOREWORD

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

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

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

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

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Public Health Service
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CONTENTS

ABSTRACT

MANGANESE (II) SULFATE MONOHYDRATE

CAS No. 10034-96-5

Chemical Formula: $MnSO_4H_2O$ Molecular Weight: 168.95

Synonyms: Manganese sulfate; manganous sulfate; sulfuric acid, manganese^{2+} salt (1:1), monohydrate

Manganese is the 12th most abundant element in the earth's crust. The base metal does not occur naturally, but is a component of more than 100 minerals, including sulfides, oxides, carbonates, silicates, phosphates, and borates. In addition to occurring in foods and drinking water, manganese occurs in the atmosphere from dust, volcanic activity, forest fires, and industrial emissions. Manganese (II) sulfate monohydrate was chosen for study because of its stability, solubility, and availability. Toxicology and carcinogenesis studies were conducted by administering manganese (II) sulfate monohydrate (97% pure) in feed to groups of male and female F344/N rats and B6C3F$_1$ mice for 14 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, germ cells of *Drosophila melanogaster*, and cultured Chinese hamster ovary cells.

14-DAY STUDY IN RATS

Groups of five male and five female rats received diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese (II) sulfate monohydrate. All rats survived to the end of the study. Male rats exposed to 50,000 ppm had a mean body weight gain 57% lower and a final mean body weight 13% lower than those of the controls. The mean body weight gain of 50,000 ppm females was 20% lower and the final mean body weight was 7% lower than those of the controls. During the second week, 50,000 ppm males and females exhibited diarrhea.

14-DAY STUDY IN MICE

Groups of five male and five female mice received diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese (II) sulfate monohydrate. One female mouse in the 25,000 ppm group died on day 1 of unknown causes; all other mice survived to the end of the study. Differences in body weights between exposed and control mice could not be attributed to chemical administration.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats received diets containing 0, 1,600, 3,130, 6,250, 12,500, or 25,000 ppm manganese (II) sulfate monohydrate. Mean daily ingestion of manganese (II) sulfate monohydrate ranged from 110 to 1,700 mg/kg body weight in males and 115 to 2,000 mg/kg in females. All rats survived to the end of the study. Mean body weight gains were marginally lower than that of controls in males exposed to 3,130 ppm or more; mean body weight gains were significantly lower than that of the controls in females exposed to 6,250, 12,500, or 25,000 ppm. At the end of the study, absolute and relative liver weights of all exposed male rats and of 25,000 ppm female rats were significantly lower than those of controls. The total leukocyte count in males was similar between exposed and control rats; however, neutrophil counts of all exposed groups were greater than those of the controls, whereas lymphocyte counts of the 6,250, 12,500, and 25,000 ppm groups were significantly lower than those of the controls. Total leukocyte counts in 6,250, 12,500, and 25,000 ppm females were significantly decreased because of a decrease in lymphocytes. Male rats also demonstrated marginal but significant increases in percent hematocrit and erythrocyte count in the 6,250, 12,500, and 25,000 ppm groups. No clinical or histopathologic findings in rats were chemical related.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice received diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese (II) sulfate monohydrate. Mean daily ingestion of manganese (II) sulfate monohydrate ranged from 330 to 7,400 mg/kg body weight in males and 390 to 6,900 mg/kg body weight in females. No deaths were chemical related. The mean body weight gains of exposed male mice and of 50,000 ppm female mice were significantly lower than those of controls. The absolute and relative liver weights of 50,000 ppm males were significantly lower than those of controls. The percent hematocrit and hemoglobin concentration of males and females exposed to 50,000 ppm were lower than those of the controls, and the mean erythrocyte volumes were significantly lower than those of the controls. The total leukocyte counts of males in the 25,000 and 50,000 ppm groups were significantly lower than that of the controls. No clinical findings were attributed to manganese (II) sulfate monohydrate ingestion. Epithelial hyperplasia and hyperkeratosis of the forestomach occurred in three 50,000 ppm males.

2-YEAR STUDY IN RATS

Groups of 70 male and 70 female rats were fed diets containing 0, 1,500, 5,000, or 15,000 ppm manganese (II) sulfate monohydrate. Based on average daily feed consumption, these doses resulted in the daily ingestion of 60, 200, or 615 mg/kg body weight (males) or 70, 230, or 715 mg/kg (females). Eight to 10 rats from each group were evaluated at 9 and 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of 15,000 ppm male rats in the 2-year study was significantly lower than that of the control group. The deaths of males in the control and exposure groups were attributed to a variety of spontaneous neoplastic and nonneoplastic lesions; however, the greater number of deaths in the 15,000 ppm group resulted from increased incidences of advanced renal disease related to ingestion of manganese (II) sulfate monohydrate. The decreased survival of the 15,000 ppm males did not occur until approximately week 93 of the study; before week 93, survival was similar in all groups. Survival of exposed females was similar to that of the controls. The mean body weight of 15,000 ppm male rats was within 5% of the control group until week 89; by week 104, the mean body weight of 15,000 ppm males was 10% lower than that of the control group. The mean body weights of 1,500 and 5,000 ppm male rats and all exposed female groups were similar to those of the controls throughout the study. Feed consumption by all exposure groups was similar to that by the control groups. No clinical findings were attributed to manganese (II) sulfate monohydrate ingestion.

Hematology, Clinical Chemistry, and Tissue Metal Concentration Analyses

No differences in hematology and clinical chemistry parameters attributable to the ingestion of manganese (II) sulfate monohydrate occurred between exposed and control groups. At both the 9- and 15-month interim evaluations, tissue concentrations of manganese were significantly elevated in the livers of 5,000 and 15,000 ppm male and female rats, with an accompanying depression of hepatic iron.

Pathology Findings

The ingestion of diets containing 15,000 ppm manganese (II) sulfate monohydrate was associated with a marginal increase in the average severity of nephropathy in male rats (0 ppm, 2.9; 1,500 ppm, 3.0; 5,000 ppm, 3.0; 15,000 ppm, 3.2). The increased severity of nephropathy in the 15,000 ppm male rats was accompanied by significantly increased incidences of mineralization of the blood vessels (4/52, 10/51, 6/51, 17/52) and glandular stomach (8/52, 13/51, 9/51, 23/52), parathyroid gland hyperplasia (14/51, 14/46, 12/49, 23/50), and fibrous osteodystrophy of the femur (12/52, 14/51, 12/51, 24/52). These lesions are manifestations of renal failure, uremia, and secondary hyperparathyroidism. The increased incidence of advanced renal disease caused reduced survival of the high-dose male rats.

No increase in the incidence of neoplasms in male or female rats was attributed to the ingestion of diets containing manganese (II) sulfate monohydrate.

2-YEAR STUDY IN MICE

Groups of 70 male and 70 female mice received diets containing 0, 1,500, 5,000, or 15,000 ppm manganese (II) sulfate monohydrate. These levels resulted in an average daily ingestion of 160, 540, or 1,800 mg/kg body weight (males) or 200, 700, or 2,250 mg/kg (females). Nine or 10 mice from each group were evaluated at the 9-month and 15-month interim evaluations.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival rates of exposed male and female mice in the 2-year study were similar to those of the control groups. The mean body weights of exposed male mice were similar to that of the control group. Compared to controls, female mice had exposure-related lower mean body weights after week 37, and the final mean body weights for the 1,500, 5,000, and 15,000 ppm groups were 6%, 9%, and 13% lower than that of the control group. Feed consumption by all exposure groups was similar to that by the control groups. No clinical findings were attributed to the administration of manganese (II) sulfate monohydrate.

Hematology, Clinical Chemistry, and Tissue Metal Concentration Analyses

No chemical-related differences between exposed and control groups occured in hematology or clinical chemistry parameters. At the 9- and 15-month interim evaluations, tissue concentrations of manganese were significantly elevated in the livers of the 5,000 and 15,000 ppm groups. Hepatic iron levels were significantly lower in exposed females at the 9-month interim evaluation and in 5,000 and 15,000 males and all exposed females at the 15-month interim evaluation.

Pathology Findings

Incidences of thyroid follicular dilatation and hyperplasia were significantly greater in 15,000 ppm male and female mice than in controls. Follicular cell adenomas occurred in one 15,000 ppm male at the 15-month interim evaluation and in three 15,000 ppm males at the end of the study but not in the lower exposure groups or the control group. Follicular cell adenomas also occurred in two control, one 1,500, and five 15,000 ppm female mice at the end of the study. It is uncertain if the slightly increased incidence of follicular cell adenoma is related to the ingestion of manganese (II) sulfate monohydrate.

The incidences of focal hyperplasia of the forestomach epithelium were significantly greater in the 15,000 ppm male and exposed female groups. The hyperplasia was associated with ulcers and inflammation in some mice, particularly males.

GENETIC TOXICOLOGY

Manganese (II) sulfate monohydrate was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation (S9), and did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*. Tests for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells treated without S9 were positive; with S9, only the sister chromatid exchange test with manganese (II) sulfate monohydrate was positive.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of manganese (II) sulfate monohydrate in male or female F344/N rats receiving 1,500, 5,000, or 15,000 ppm. There was *equivocal evidence of carcinogenic activity* of manganese (II) sulfate monohydrate in male and female B6C3F_1 mice, based on the marginally increased incidences of thyroid gland follicular cell adenoma and the significantly increased incidences of follicular cell hyperplasia.

The ingestion of diets containing manganese (II) sulfate monohydrate was associated with an increased severity of nephropathy in male rats, focal squamous hyperplasia of the forestomach in male and female mice, and ulcers and inflammation of the forestomach in male mice. These studies were not designed to assess any neurotoxicity that might have been expected with chronic exposure to sufficiently high doses of manganese.

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

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Manganese (II) Sulfate Monohydrate

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 1,500, 5,000, or 15,000 ppm in feed (equivalent to 60, 200, or 615 mg/kg body weight per day)	0, 1,500, 5,000, or 15,000 ppm in feed (equivalent to 70, 230, or 715 mg/kg body weight per day)	0, 1,500, 5,000, or 15,000 ppm in feed (equivalent to 160, 540, or 1,800 mg/kg body weight per day)	0, 1,500, 5,000, or 15,000 ppm in feed (equivalent to 200, 700, or 2,250 mg/kg body weight per day)
Body weights			
15,000 ppm group lower than controls	Exposed groups similar to controls	Exposed groups similar to controls	Exposed groups lower than controls
2-Year survival rates			
25/52, 17/51, 21/51, 7/52	37/50, 37/50, 42/50, 36/48	45/50, 44/50, 46/51, 46/50	42/50, 46/50, 38/50, 42/51
Nonneoplastic effects			
Kidney: nephropathy severity (2.9, 3.0, 3.0, 3.2)	None	Thyroid gland: follicular cell focal hyperplasia (5/50, 2/49, 8/51, 27/50) Forestomach: focal squamous hyperplasia (2/50, 1/49, 5/51, 14/50); ulcer: (0/50, 0/49, 0/51, 6/50); inflammation: (0/50, 0/49, 0/51, 5/50)	Thyroid gland: follicular cell focal hyperplasia (3/50, 15/50, 27/49, 43/51) Forestomach: focal squamous hyperplasia (1/51, 3/50, 3/49, 9/50)
Uncertain effects			
None	None	Thyroid gland: follicular cell adenoma (0/50, 0/49, 0/51, 3/50)	Thyroid gland: follicular cell adenoma (2/50, 1/50, 0/49, 5/51)
Level of evidence of carcinogenic activity			
No evidence	No evidence	Equivocal evidence	Equivocal evidence
Genetic toxicology			
Salmonella typhimurium gene mutation:		Negative in strains TA97, TA98, TA100, TA1535, and TA1537 with and without S9	
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:		Positive with and without S9	
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:		Positive without S9; negative with S9	
Sex-linked recessive lethal mutations *Drosophila melanogaster*:		Negative when administered in feed or by injection	

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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 manganese (II) sulfate monohydrate on June 23, 1992, 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.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 23, 1992, the draft Technical Report on the toxicology and carcinogenesis studies of manganese (II) sulfate monohydrate 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.

Mr. J.D. Cirvello, NIEHS, introduced the toxicology and carcinogenesis studies of manganese (II) sulfate monohydrate by discussing the occurrence, uses and rationale for study of manganese, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplasms in mice and nonneoplastic lesions in rats and mice. The proposed conclusions were *no evidence of carcinogenic activity* of manganese (II) sulfate monohydrate in male or female F344/N rats and *equivocal evidence of carcinogenic activity* in male and female B6C3F_1 mice.

Dr. van Zwieten, a principal reviewer, agreed with the proposed conclusions. He suggested that photomicrographs illustrating some of the thyroid lesions observed in mice would be a useful addition to the report.

Dr. Zeise, the second principal reviewer, agreed in principle with the proposed conclusions, adding that it appeared that the maximum tolerated dose was not reached for female rats and male mice.

Dr. R.A. Griesemer, NIEHS, contrasted the lack of neurologic effects of manganese in rodents with characteristic neurotoxicity in humans. He noted that the effects found in humans are related to the neuromelanin-containing parts of the brain, and rats and mice do not have neuromelanin. Dr. Silbergeld stated that since manganese is a known neurotoxin, the National Toxicology Program should have incorporated specific measures of neurobehavioral assessment into the experimental design.

Dr. Hayden commented that the only indication of a carcinogenic effect in male rats was in pancreatic islet cells in which the incidences of hyperplasia and adenoma were slightly higher in exposed groups. Since manganese preferentially accumulates in tissues rich in mitochondria with islet cells among the richest, Dr. Hayden said there might be a correlation

Dr. J. Haartz, NIOSH, asked if the actual oxidation state of manganese in the animal diet is known, because manganese is rather easily oxidized and oxidation state plays a role in the carcinogenicity of certain metals. Dr. T.J. Goehl, NIEHS, confirmed the oxidation state.

Dr. van Zwieten moved that the Technical Report on manganese (II) sulfate monohydrate be accepted with the revisions discussed and with the conclusions as written for male and female rats, *no evidence of carcinogenic activity*, and for male and female mice, *equivocal evidence of carcinogenic activity*. Dr. Zeise seconded the motion. Dr. Zeise then offered an amendment to add a statement that female rats and male mice might have tolerated higher dose levels. Dr. Bailey seconded the motion, which was defeated by five no votes with one abstention (Dr. Silbergeld) to two yes votes (Drs. Bailey and Zeise). Dr. Silbergeld said she abstained because the study was wholly inadequate to assess toxicity, so it was impossible to determine an overall dose response. Dr. Silbergeld offered an amendment that the following sentence be added to the end of the second paragraph of the conclusions: "The study was inadequate to detect or assess any neurotoxicity that would have been expected to be associated with chronic manganese exposure." Dr. Davis seconded the motion, which was accepted by six yes to two no votes (Drs. Davidson and Goodman). The original motion by Dr. Van Zwieten as amended by Dr. Silbergeld was accepted unanimously with eight votes.

INTRODUCTION

MANGANESE (II) SULFATE MONOHYDRATE

CAS No. 10034-96-5

Chemical Formula: $MnSO_4H_2O$ Molecular Weight: 168.95

Synonyms: Manganese sulfate; manganous sulfate; sulfuric acid, manganese^{2+} salt (1:1), monohydrate

CHEMICAL AND PHYSICAL PROPERTIES

Manganese (II) sulfate monohydrate is a white, slightly efflorescent crystalline compound that dehydrates at 400° to 450° C and is stable up to 850° C. Manganese (II) sulfate monohydrate is soluble in water and insoluble in alcohol (*Kirk-Othmer*, 1981; *Merck Index*, 1989).

USE AND HUMAN EXPOSURE

Manganese is the 12th most abundant element in the earth's crust and is present in soil, rocks, sediments, and water. The base metal does not occur naturally but is a component of more than 100 minerals, including sulfides, oxides, carbonates, silicates, phosphates, and borates. Pyrolusite (manganese dioxide), rhodochrosite (manganese carbonate), and rhodonite (manganese silicate) are the most commonly occurring manganese-bearing minerals (*Merck Index*, 1989).

The primary use of elemental manganese is in metallurgical processing and approximately 90% is used in steel manufacturing. Domestic consumption of manganese sulfate in 1988 was estimated at 14,000 to 14,500 tons. Of that amount, approximately 60% was used in micronutrient fertilizer, primarily for citrus fruit; an estimated 30% was used as a trace mineral in animal feeds, especially for poultry (*Chemical Marketing Reporter*, 1988). Manganese is considered an essential element and the sulfate salt is used as a nutrient and dietary supplement for humans and other animals. Manganese (II) sulfate monohydrate is also used for red glazes on porcelain, in dyes, in fertilizers for vine crops and tobacco, and in boiling oils for varnishes. The chemical is produced by dissolving manganese carbonate ore or manganese II oxide in sulfuric acid; prior to 1986 it was also obtained as a byproduct in the manufacturing process of hydroquinone (*Kirk-Othmer*, 1981).

Because of its ubiquitous nature, manganese is commonly found in food and drinking water. Humans ingest manganese from three main sources: diet, drinking water, and inhaled particles cleared from the respiratory tract (USEPA, 1984a). Natural occurrences including continental dust, volcanic gas and dust, and forest fires are the principal sources of manganese in the atmosphere (USEPA, 1984b). Anthropogenic manganese emissions to the air are mainly from the production of ferroalloys, iron, and steel. Fossil fuel combustion is also an important source because of the volume of coal burned each year. Atmospheric manganese may occur as coarse dusts containing low concentrations of manganese as oxides, hydroxides, or carbonates ($\leq$ 1 mg Mn/g). Manganese from smelting or combustion processes is often present in fine particles with high concentrations of manganese as oxides (as high as 250 mg/g). Organic manganese is usually not present in detectable concentrations. Atmospheric reactions of manganese oxides with sulfur dioxide or nitrogen dioxide are thought to produce the divalent sulfate or nitrate salts. The combustion of leaded gasoline, which contains methylcyclopentadienyl manganese tricarbonyl as an additive, also contributes a small amount of manganese to the atmosphere (Davis *et al.*, 1988). In public water supplies a median concentration of 4 μg/L has been reported (USEPA, 1984a).

Food is the major source of manganese for the general population; however, since manganese concentrations in foodstuffs vary widely and dietary habits differ, determining an average daily intake is difficult; an estimate of 3.8 mg a day for 15- to 18-year-old males has been made (USEPA, 1984a). The dietary needs of humans are assumed to be in the range of 3 to 7 mg a day (*Kirk-Othmer*, 1981). In areas without manganese-emitting industries, daily exposure to manganese from air has been estimated to be lower than 4 μg/day; whereas in areas with an emission source, the maximum daily

exposure can be up to 200 μg/day (Saric, 1986). The highest ambient air concentrations of manganese were seen in the 1960's in areas of ferromanganese manufacturing, with levels exceeding 10 $\mu g/m^3$; more recent measurements indicated that decreases of at least an order of magnitude had occurred (USEPA, 1984a). Occupational exposures to manganese are highest in mines, but no appreciable amount is mined in the United States. Values in the range of 5 to 8 mg/m^3, and occasionally up to 20 mg/m^3, were found in dry cell battery and ferromanganese plants (Saric, 1986). The Occupational Safety and Health Administration has established a Permissible Exposure Limit (PEL) of 5 mg/m^3 for manganese compounds in the workplace; for manganese fumes and certain specific compounds, the PEL varies. From a survey conducted from 1981 to 1983, NIOSH estimated that 300 workers in the U.S. were potentially exposed to pure manganese and 630,000 workers to other forms of manganese; this survey also estimated that 893 workers at 60 plants were potentially exposed to manganese (II) sulfate monohydrate (NIOSH, 1990).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Manganese is a cofactor essential for the activity of many cellular enzymes such as pyruvate carboxylase, arginase, and phosphatase. Absorption from the gastrointestinal tract is poor under normal conditions because of the low solubility of cationic manganese. At the alkaline pH of the small intestine, Mn^{2+} is converted into Mn^{3+}, and absorption of Mn^{3+} depends on the intestinal manganese concentration and the level and form of the manganese and organic chelates in the body. Iron deficiency increases manganese absorption, whereas absorption is reduced by excess dietary calcium or phosphorus. Absorbed manganese is transported to the liver, conjugated with bile, and excreted into the intestine, where part of the manganese is reabsorbed into the enterohepatic circulation. The lower valence oxides of manganese are poorly absorbed. Manganese absorption from sites of parenteral administration is slow but continuous until complete absorption occurs. Soluble manganese chelates are absorbed rapidly. Inhaled manganese salts are deposited in the lungs, where slow but continuous absorption takes place, the rate depending on the body manganese reserves. Some of the manganese absorbed from the lung is transferred to the gastrointestinal tract and reabsorbed. The gastrointestinal tract is the effective route of entry and excretion whether manganese is ingested or inhaled. Although absorption of cationic manganese by the skin is poor, organic manganese compounds are absorbed rapidly (Venugopal and Luckey, 1978).

Turnover of manganese in mammalian tissues is rapid, depending on the exogenous supply. Absorbed manganese is retained initially by mitochondria in the liver, pancreas, and kidneys. About 40% of the total body content of manganese is retained in the bone marrow, and the rest is in a freely exchangeable, labile pool. The uniform manganese concentration in mammals and the lack of accumulation with age are due to an efficient homeostasis that regulates manganese excretion more than absorption. Manganese excretion is almost exclusively fecal and involves the liver, pancreas, and intestinal wall. If manganese is administered as soluble and stable manganese chelates, approximately 6% is excreted in the urine. Under normal conditions, other metal ions do not affect manganese metabolism (Venugopal and Luckey, 1978).

Humans

Manganese deficiency has not been clearly demonstrated in humans. In humans, the liver, pancreas, kidneys, and intestines are specific tissues for manganese retention (Saric, 1986).

TOXICITY

Experimental Animals

Among the essential trace elements, manganese is considered the least toxic. Venugopal and Luckey (1978) state that mice, rats, and rabbits can tolerate approximately 1,000 ppm Mn^{2+} in the diet or drinking water; however, the length of time is not specified. Interference with iron metabolism, specifically hemoglobin formation, is one of the first toxic effects noticed (*Kirk-Othmer*, 1981). The average LD_{50} observed in different animal experiments indicates that the oral dose values range from 400 to 830 mg of manganese per kilogram of body weight for soluble manganese compounds, much higher than the 38 to 64 mg of manganese per kilogram of body weight for parenteral injection (USEPA, 1984a).

In animal studies, marked degenerative changes in the seminiferous tubules were found in rats and rabbits exposed to high levels of manganese (Chandra *et al.*, 1973; Shukla and Chandra, 1977). Chronic exposure to

manganese oxide in the diet at 1,050 ppm caused retarded sexual development in male mice (Gray and Laskey, 1980). Subcutaneous injection of 150 mg manganese per kilogram of body weight produced significant increases in percent hematocrit and mean cell volume in rats, while serum calcium and iron were markedly depressed (Baxter *et al.*, 1965). Similar findings occurred when rabbits were exposed to manganese dioxide in inhalation chambers (Doi, 1959). Conversely, depressed hemoglobin formation was found in animals exposed to manganese in the diet (Hartman *et al.*, 1955; Matrone *et al.*, 1959). Marked degenerative changes in the adrenal cortex, with an increase in cholesterol content, were found in rabbits administered manganese chloride intravenously in doses of 2.5 mg/kg body weight (Chandra and Imam, 1975). In rats, exposure to 0.7 to 2.0 mg manganese sulfate in feed may result in depressed thyroid activity, reduced thyroid weight, and thinning of follicular epithelium (Khakimova *et al.*, 1969).

Humans

In humans, acute systemic intoxication rarely occurs after oral administration. "Metal fume fever" is an acute effect of occupational inhalation of manganese or other metals in aerosols or fine dusts. The syndrome begins 4 to 12 hours after sufficient exposure, with symptoms mimicking influenza, and usually lasts 24 hours without producing permanent damage (Piscator, 1976). Following inhalation of dusts of manganese oxides approximately 3 μm in size for a few months, industrial workers develop pulmonary pneumonitis (Venugopal and Luckey, 1978). In a review of the literature pertaining to the effects of manganese in the lungs of animals, Saric (1986) concluded that the available data were insufficient for estimating the exact lung effects of manganese and particularly the dose-response relationship. Besides parenteral routes, systemic poisoning may result from chronic inhalation or chronic ingestion. Occupational exposure to manganese for periods from 6 months to 2 years can result in manganism, a disease of the central nervous system characterized by psychogenic and neurological disorders with symptoms resembling Parkinson's disease. Permanent damage to the ganglion cells of the basal ganglia at exposure levels that do not otherwise produce an effect (Gosselin *et al.*, 1984) and a reduction of endogenous dopamine in the caudate nucleus (Neff *et al.*, 1969) further substantiate a parkinsonian-like syndrome. The epidemiologic data regarding manganism have come from exposures to manganese at a variety of industrial operations such as ore crushing and packing, ferroalloy production, the use of manganese in steel production, the manufacture of dry cell batteries, welding rod manufacture, and manganese mining. Thus, the particle size, concentration, and chemical form of manganese to which workers developing manganism have been exposed varies widely, making the establishment of a dose-response relationship difficult. A review of the epidemiology studies leads to the conclusion that no substantial evidence of chronic manganese poisoning exists at exposures less than 5 mg/m^3.

Cases diagnosed as manganism have been found in workers in mines with airborne manganese concentrations of 40 to 250 mg/m^3 or higher, but occasionally also in mines with lower concentrations. In a ferromanganese plant, manganism has occurred at exposure levels of 2.1 to 12.9 mg/m^3 and cases of slight neurological abnormalities have occurred at manganese exposure concentrations of 0.3 to 20 mg/m^3. A number of workers exposed at other facilities, such as dry cell battery plants, had symptoms of the disease at exposure levels of 1.9 to 28.4 mg/m^3 (Saric, 1986). The existing data on the effects of manganese on human blood conflict. A reduced white cell count was found in a number of workers affected by manganese exposure (Flinn *et al.*, 1941; Faught, 1946). In other studies, small doses of manganese had a stimulatory effect on erythropoiesis (Kesic and Häusler, 1954; Paterni, 1954). In findings related to chronic manganese exposure, large amounts of manganese caused depression of both erythropoiesis and granulocyte formation (Rodier, 1955; Cotzias, 1958).

Impotence has often been reported in workers affected by manganese exposure (Venugopal and Luckey, 1978). A disruption in the excretion of 17-ketosteroids was also found in patients with chronic manganese exposure (Jonderko *et al.*, 1971).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Little conclusive evidence was found in the literature regarding the teratogenicity of manganese. Impairment of geotaxis performance, but not intelligence, was reported in mice treated *in utero* with manganese (Hoshishima *et al.*, 1977). In another study, female mice were exposed to manganese dioxide dust (48.9 ± 7.5 g/m^3, continuous exposure) from days 0 through 18 of pregnancy (Massaro *et al.*, 1980). No significant differences in pup weight or activity were found whether the pup had been exposed *in utero* or not, but as adults, pups exposed *in utero* were deficient in open-field, exploratory, and rotarod (balance and coordination) performance. Pups not exposed *in utero* fostered to exposed mothers also showed decreased rotarod performance, indicating that postpartum exposure can also have an adverse effect on behavioral development. Additional evidence that may have some bearing on this result is reported in a study of the effect of manganese on learning in the adult rat (Murthy *et al.*, 1981). The findings in a study of the distribution of ^{54}Mn in fetal, young, and adult rats may also relate to the above results (Kaur *et al.*, 1980). Early neonates and 19-day fetuses were more susceptible to manganese than the older groups; manganese was localized in the liver and brain of the younger groups and more manganese per gram of body weight was accumulated than in the older groups. No fetal abnormalities occurred when 18-day embryos were exposed to 16 μmol/200 g maternal weight.

A teratologic evaluation of manganese (II) sulfate monohydrate was conducted in rats, mice, hamsters, and rabbits using the following gavage dose ranges for 10 consecutive days: rats 0.783 to 78.3 mg/kg; mice 1.25 to 125 mg/kg; hamsters 1.36 to 136 mg/kg; rabbits 1.12 to 112 mg/kg (NTIS, 1973). No clearly discernible effect on nidation or on maternal or fetal survival was found, and the number of abnormalities in either soft or skeletal tissues of the test groups did not differ from the control animals.

The effect of dietary manganese on the content of manganese, iron, copper, and zinc in maternal and fetal tissues was studied in female Sprague-Dawley rats (Järvinen and Ahlström, 1975). Diets containing 4, 24, 54, 154, 504, or 1,004 mg manganese per kg feed were administered from the time of weaning. The animals were mated and the offspring collected by cesarean section at day 21 of pregnancy. Concentrations of manganese were higher in the livers of pregnant rats with the highest manganese intake; whereas in nonpregnant animals, the dietary manganese level had no appreciable effect on manganese concentrations in the liver. However, the iron content of the livers of both pregnant and nonpregnant rats fell as the manganese level of the diet increased. The manganese content was highest and the iron content was lowest in the offspring of dams exposed to the largest amounts of manganese. No gross malformations or bone structure anomalies occurred in the fetuses at any dose level.

Humans

No information on the reproductive or developmental toxicity of manganese (II) sulfate monohydrate in humans was found in the literature.

CARCINOGENICITY

Experimental Animals

Manganese (II) sulfate in physiological saline was tested for carcinogenic activity in the strain A mouse lung tumor model (Stoner *et al.*, 1976). In this study, male and female mice, 6 to 8 weeks old, were injected intraperitoneally three times a week with doses of 132, 330, or 660 mg manganese (II) sulfate/kg of body weight for a total of 22 injections. Ten male and 10 female mice were used for each dose level and for a vehicle (saline) and a positive (urethane) control group. Mice were killed 30 weeks after the first injection. A slight increase (P=0.068, Fisher exact test) in the number of pulmonary adenomas per mouse was associated with administration of the high dose. The response at the other doses was similar to that of the vehicle controls. Subsequent studies, however, have questioned the capability of the strain A model to detect carcinogenicity. In a study by Smith and Witschi (1984) of 18 known human carcinogens, only five were unequivocally positive in the lung tumor assay.

DBA mice were injected subcutaneously or intraperitoneally with 0.1 mL of a 1% manganese chloride aqueous solution twice weekly for 6 months (DiPaolo, 1964). Mice were killed as they became moribund or at 18 months of age. Sixty-seven percent (24/36) of the mice treated subcutaneously and 41% (16/39) of the mice treated intraperitoneally developed lymphosarcomas compared with 24% of the control group.

A study was conducted to evaluate the carcinogenicity of manganese powder and manganese dioxide in F344 rats and Swiss mice, and manganese (II) acetylacetonate in F344 rats (Furst, 1978). Trioctanoin suspensions of manganese dioxide and manganese powder were administered intramuscularly to rats (monthly for 9 months) and mice (a single injection of manganese powder; six monthly injections of 3 mg manganese dioxide; six monthly injections of 5 mg manganese dioxide), and manganese powder was also administered by gavage (twice monthly for 12 months) to the rats. No difference in neoplasm incidence was noted between treated and control animals during 2 years. In contrast, manganese (II) acetylacetonate administered intramuscularly to rats (monthly for 9 months) produced a statistically significant number of fibrosarcomas at the sites of injection. After the positive results were obtained, another experiment was conducted with manganese powder administered orally (twice monthly for 12 months); rats received approximately 3.75 times as much manganese as was present in the organomanganese compound and no neoplasms developed after 2 years.

Studies by other investigators indicated that single intramuscular injections of penicillin suspensions containing manganese dust did not induce injection site neoplasms in Fischer rats (Sunderman *et al.*, 1974, 1976). The results of other experiments in these studies indicated that the addition of equimolar amounts of manganese dust to nickel subsulfide (Ni_3S_2) dust significantly depressed Ni_3S_2 induced tumorigenesis. However, subsequent studies (Sunderman and McCully, 1983) demonstrated that when manganese dust was injected in one thigh of a rat and Ni_3S_2 in the opposite thigh of the same animal, no inhibitory effect on tumorigenesis occurred, and the conclusion was that inhibition of neoplasms by manganese dust is a local rather than systemic effect. Additional findings were that, with the possible exception of manganese sulfide, other manganese compounds tested (manganese sesquioxide, manganese dioxide, and manganese carbonyl) did not inhibit the tumorigenicity of nickel subsulfide. The same group of investigators showed that manganese dust inhibited local sarcoma induction by benzo(a)pyrene.

Humans

No information was found regarding the carcinogenicity of manganese or its compounds in humans. A cohort of 3,961 men employed at three ferromanganese plants in Norway was followed from 1953 to 1982, and no increased cancer incidence was reported (Kjuus *et al.*, 1986).

GENETIC TOXICITY

The results of genetic toxicity tests with manganese (administered as various salts) were mixed. Detection of manganese mutagenicity appears dependent on the particular assay system and the protocol used. In standard bacterial assays, manganese sulfate did not induce gene mutations in *Salmonella typhimurium* (Newell *et al.*, 1974; Marzin and Phi, 1985; Mortelmans *et al.*, 1986) or SOS DNA repair processes in *Escherichia coli* (Olivier and Marzin, 1987) but was weakly positive in the *Bacillus subtilis* Rec assay for growth inhibition due to DNA damage (Newell *et al.*, 1974; Nishioka, 1975). Pagano and Zeiger (1992) have shown that in the standard assays, components of the culture media inhibit the mutagenic activity of metal ions by chelating these ions or by competition for active transport sites. Therefore, the lack of mutagenicity in some bacterial assays may be due to the lack of bioavailability of the metal ion, not to the insensitivity of the bacteria to the genetic effects of Mn^{2+}. Conducting *S. typhimurium* mutation assays with a modified preincubation protocol in which distilled, deionized water was substituted for the standard sodium phosphate buffer allowed the detection of manganese mutagenicity (Pagano and Zeiger, 1992). In assays with yeast, weakly positive results with manganese were reported for gene mutation (Singh, 1984), and both weakly positive (Singh, 1984) and negative (Baranowska *et al.*, 1977; Parry, 1977) results were reported for gene conversion. Manganese administered as a salt at nontoxic levels induced forward mutations at the hypoxanthine guanine phosphoribosyltransferase locus in cultured Chinese hamster V79 cell cultures (Zelikoff *et al.*, 1986). No increase in sex-linked recessive lethal mutations was observed in germ cells of *Drosophila melanogaster* administered manganese (II) sulfate monohydrate by feeding or by injection (Valencia *et al.*, 1985).

Exposure of cultured Chinese hamster ovary cells and human fibroblast cell cultures to high concentrations (10 mM) of manganese chloride resulted in the formation of DNA strand breaks (Hamilton-Koch *et al.*, 1986). Cultured Chinese hamster ovary cells were shown to be markedly more sensitive to the toxic effects of manganese, although comparative uptake of the metal was similar between the two cell types. Significant increases in sister chromatid exchanges were seen in

mouse fibroblasts (Andersen, 1983), cultured Chinese hamster ovary cells (Galloway *et al.*, 1987), and human lymphocytes (Andersen, 1983) treated with manganese sulfate without exogenous metabolic activation (S9). Chromosomal aberrations were also induced in cultured Chinese hamster ovary cells following treatment with manganese sulfate without S9 (Galloway *et al.*, 1987). The cytogenetic effects observed in cultured Chinese hamster ovary cells were accompanied by severe cytotoxicity. No induction of heritable translocations in mice or dominant lethal mutations in rats were observed following administration gavage once a day for 1 to 5 days (rats) (Newell *et al.*, 1974).

STUDY RATIONALE

The National Cancer Institute nominated manganese for evaluation because of its reported carcinogenicity in mice, mutagenicity in several *in vitro* systems, and widespread human exposure. Manganese (II) sulfate monohydrate was chosen as the specific compound for testing due to stability, solubility, availability, and use of the sulfate as a food supplement for humans and animals.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF MANGANESE (II) SULFATE MONOHYDRATE

Manganese (II) sulfate monohydrate was obtained in one lot (003261) from the J.T. Baker Chemical Company (Glen Ellyn, IL). Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of manganese (II) sulfate monohydrate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white, slightly efflorescent crystalline compound, was identified as manganese (II) sulfate monohydrate by infrared and ultraviolet/visible spectroscopy. The infrared spectrum matched a literature reference (Miller and Wilkins, 1952), and the absence of a signal in the visible spectrum indicated that no manganate (VI) or permanganate (VII) species were present. The purity was determined by elemental analyses, weight loss on drying, chelometric titration, and spark source mass spectroscopy. Elemental analyses for manganese, sulfur, and hydrogen were in reasonable agreement with theoretical values for manganese (II) sulfate monohydrate. Weight loss on drying indicated 10.6% ± 0.01% water, consistent with a theoretical value of 10.7% for manganese (II) sulfate monohydrate. Spark source mass spectrometry confirmed manganese as the major component. The most significant impurities were sodium (640 ppm), potassium (120 ppm), and silicon (160 ppm). Chelometric titration indicated a purity of 97.7% ± 0.4%. The overall data indicated that the manganese was in the divalent state and supported a purity of greater than 97%.

The divalent state of manganese is the most common form of this element and is stable in neutral or acid medium. Because of the physical and chemical properties of manganese (II) sulfate monohydrate, no bulk chemical stability studies were performed. In accordance with analytical chemistry laboratory recommendations, the bulk chemical was stored in the dark at room temperature throughout the studies. Periodic monitoring of the chemical by the study laboratory using chelometric titration and elemental analyses (Galbraith Laboratories, Inc., Knoxville, TN) indicated no degradation of the bulk chemical during the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared by mixing manganese (II) sulfate monohydrate with feed (Table I1). Homogeneity and stability analyses of the dose formulations were conducted by the analytical chemistry laboratory using a spectrophotometric method. Homogeneity was confirmed; stability of the dose formulations was established for 2 weeks in the dark at room temperature and for 1 week exposed to air and light. A subsequent study confirmed the stability of the dose formulations for 3 weeks under the conditions listed above. No direct speciation was performed. However, complete recovery from dose formulations was achieved and other likely species are not soluble in dilute acid which was used for extraction. These findings strongly support the conclusion that the manganese remained in the divalent state. The dose formulations were prepared once for the 14-day studies and weekly for the 13-week and 2-year studies. Dose formulations were discarded 21 days after the date of preparation.

Periodic analyses of the dose formulations of manganese (II) sulfate monohydrate were conducted at the study laboratory and at the analytical chemistry laboratory using spectrophotometric methods. Dose formulations were analyzed once during the 14-day studies, three times during the 13-week studies, and every 2 months during the 2-year studies. All dose formulations for rats and mice were within the specified 10% of the target concentrations throughout the studies (Tables I2 through I4). Results of periodic referee analyses performed by the analytical chemistry laboratory were also within 10% of the target concentrations (Table I5).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories

(Portage, MI). At receipt, the rats were an average of 31 days old, and the mice were an average of 35 days old. The rats were quarantined for 19 days and the mice for 20 days before exposure began. Before the beginning of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats and mice were fed diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese (II) sulfate monohydrate. The level of manganese in the diet received by controls was approximately 92 ppm. The appropriate feed was supplied twice weekly and was available *ad libitum*. Clinical findings for rats were recorded daily days 1 to 8, then twice daily days 9 to 14; clinical findings for mice were recorded twice daily. Feed consumption was recorded weekly by cage. The animals were weighed at study initiation, on day 7, and at the end of the studies. Details of study design and animal maintenance are summarized in Table 1.

At the end of the 14-day studies, blood from the vena cava of all animals was collected for hematology analyses. The hematology parameters measured are listed in Table 1. A gross necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, left testicle, and thymus were weighed. Tissue samples of the livers from high-dose and control rats and mice were collected for manganese concentration analyses. Histopathologic examinations were not conducted.

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to manganese (II) sulfate monohydrate and to determine the appropriate exposures to be used in the 2-year studies.

Male and female F344/N rats were obtained from the Charles River Breeding Laboratories (Stone Ridge, NY) and male and female B6C3F$_1$ mice were obtained from Simonsen Labs, Inc. (Gilroy, CA). On receipt, the rats were an average of 31 days old and the mice were an average of 43 days old. The rats were quarantined for 19 days and the mice for 20 days before exposure began. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five control animals of each species and sex using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats were fed diets containing 0, 1,600, 3,130, 6,250, 12,500, or 25,000 ppm manganese (II) sulfate monohydrate. Groups of 10 male and 10 female mice were fed diets containing 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm manganese (II) sulfate monohydrate. The level of manganese in the diet received by controls was approximately 92 ppm. The appropriate feed was supplied twice weekly and was available *ad libitum*. Clinical findings were recorded weekly. Feed consumption was recorded weekly by cage. The rats were weighed at the beginning of the studies and weekly thereafter; mice were weighed initially and twice weekly thereafter. Further details of study design and animal maintenance are summarized in Table 1.

At the end of the 13-week studies, blood was collected from the vena cava of all animals for hematology analyses. The hematology parameters measured are listed in Table 1. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, left testicle, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control and high-dose animals. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 70 male and 70 female rats and mice were fed diets containing 0, 1,500, 5,000, or 15,000 ppm manganese (II) sulfate monohydrate for 103 weeks. The level of manganese in the diet received by controls was approximately 92 ppm. As many as 10 rats and 10 mice per group were evaluated after 9 months and 15 months of chemical exposure.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) for use in the 2-year studies. Rats were quarantined for 12 days, and mice were quarantined for 13 days before the beginning of the studies. Five rats and five mice

of each sex were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice in the 2-year studies were approximately 41 days old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

Animal Maintenance

Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Feed consumption was measured for 7 days, once a month. Cages were rotated every 2 weeks; racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition is provided in Appendix K.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly for the first 13 weeks and monthly thereafter. The brain, kidneys, and liver from animals selected for the 9- and 15-month evaluations were weighed at necropsy. Tissues examined in metal concentration analyses for copper, iron, manganese, and zinc were blood plasma (rats), brain, kidney, liver, and pancreas.

All animals were necropsied. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. Complete histopathologic examinations were performed on 0 and 15,000 ppm animals at the 9- and 15-month interim evaluations and gross lesions were examined for the 1,500 and 5,000 ppm groups. Complete histopathologic examinations were performed on all animals surviving until the end of the studies and on those that died or were killed moribund during the studies. Tissues examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the pancreas of male and female rats, the kidney of male rats, the forestomach and thyroid gland of male and female mice, and the pituitary gland of female mice.

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

Statistical Methods

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B4, C1, C5, D1, and D5 are given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of all nonneoplastic lesions and most neoplasms (Tables A3, B3, C3, and D3)

are also given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

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

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

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

Analysis of Nonneoplastic Lesion Incidences

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry and hematology data and tissue metal concentrations, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-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 or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

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

Quality Assurance Methods

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

GENETIC TOXICOLOGY

The genetic toxicity of manganese (II) sulfate monohydrate was assessed by testing its ability to induce mutations in various strains of *Salmonella typhimurium* and in germ cells of male *Drosophila melanogaster* and to induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of manganese (II) sulfate monohydrate 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 of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between the potential electrophilicity of a chemical (structural alert to DNA reactivity), mutagenicity in *S. typhimurium*, and carcinogenicity in rats and mice at single or 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), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical under investigation. Data from NTP studies show that a positive response in *S. typhimurium* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the mutagens were rodent carcinogens), and that there is no complimentarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *S. typhimurium* test improved the predictivity of the *S. typhimurium* test alone. The predictivity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Manganese (II) Sulfate Monohydrate

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Gulf South Research Institute (New Iberia, LA)	Gulf South Research Institute (New Iberia, LA)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Rats: Charles River Breeding Laboratories (Stone Ridge, NY) Mice: Simonsen Labs, Inc. (Gilroy, CA)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Studies		
Rats: 19 days Mice: 20 days	Rats: 19 days Mice: 20 days	Rats: 12 days Mice: 13 days
Average Age When Studies Began		
Rats: 50 days Mice: 55 days	Rats: 50 days Mice: 63 days	Rats: 41 days Mice: 41 days
Date of First Dose		
Rats: 1 February 1982 Mice: 29 March 1982	30 August 1982	Rats: 24 September 1984 Mice: 8 October 1984
Duration of Dosing		
14 days	Rats: 93-94 days Mice: 90-91 days	103 weeks
Date of Last Dose		
Rats: 15 February 1982 Mice: 14 April 1982	Rats: 1, 2 December 1982 Mice: 29, 30 November 1982	Rats: 14 September 1986 Mice: 28 September 1986
Necropsy Dates		
Rats: 15 February 1982 Mice: 14 April 1982	Rats: 1-2 December 1982 Mice: 29-30 November 1982	Rats 9-Month interim: 25-26 June 1985 15-Month interim: 4 December 1985 Terminal: 22-25 September 1986 Mice 9-Month interim: 10-11 July 1985 15-Month interim: 2-3 January 1986 Terminal: 6-10 October 1986

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Manganese (II) Sulfate Monohydrate (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Average Age at Necropsy Rats: 65 days Mice: 72 days	Rats: 20-21 weeks Mice: 22 weeks	9-Month interim: 45 weeks 15-Month interim: 68 weeks (rats) and 70 weeks (mice) Terminal: 110 weeks
Size of Study Groups 5 males and 5 females	10 males and 10 females	70 males and 70 females
Method of Distribution Animals were grouped by weight intervals. Animals from each interval were randomized and proportionately assigned to cages, then the cages were assigned to dose groups using an appropriate table of random numbers.	Same as 14-day studies	Same as 14-day studies
Animals per Cage 5	5	5
Method of Animal Identification Ear punch/notch and toe clip	Ear clip/notch and toe clip	Toe mark
Diet* NIH-07 open formula meal rat and mouse diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Maximum Storage Time for Feed 90 days	90 days	120 days
Water Automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly	Same as 14-day studies	Same as 14-day studies
Bedding Heat-treated hardwood chips (PWI, Inc., Loweville, NY), changed twice weekly	Same as 14-day studies	BetaChips, hardwood chips (Northeastern Products, Inc., Warrensburg, NY), changed twice weekly or more frequently when needed

* NIH-07 diet contains 60 g manganous oxide per 2,000 lbs feed.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Manganese (II) Sulfate Monohydrate (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Cage Filters		
Spun-bonded polyester (Lab Products, Inc., Garfield, NJ), changed once every 2 weeks	Same as 14-day studies	Spun-bonded, DuPont 2024 polyester (Snow Filtration Co., Cincinnati, OH), changed once every 2 weeks
Racks		
Stainless steel (Lab Products, Inc., Garfield, NJ), changed once every 2 weeks	Same as 14-day studies	Same as 14-day studies
Animal Room Environment		
Temperature: 23.3° ± 2° C Relative humidity: 40 - 80% Fluorescent light: 12 hours/day Room air: 12 changes/hour	Same as 14-day studies	Temperature: 20.6° - 23.9° C Relative humidity: 35 - 65% Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm in feed, available *ad libitum*	Rats: 0, 1,600, 3,130, 6,250, 12,500, or 25,000 ppm in feed, available *ad libitum* Mice: 0, 3,130, 6,250, 12,500, 25,000, or 50,000 ppm in feed, available *ad libitum*	0, 1,500, 5,000, or 15,000 ppm in feed, available *ad libitum*
Type and Frequency of Observation		
Observed and observations recorded once daily on days 1-8, twice daily on days 9-14 (rats) or twice daily (mice). Animals weighed initially, at the end of 1 week, and at end of the studies. Feed consumption recorded weekly by cage.	Observed once weekly. Clinical observations recorded once weekly. Animals weighed initially, once weekly (rats) or twice weekly (mice), and at end of study. Feed consumption recorded weekly by cage.	Observed twice daily. Clinical observations and animal weights recorded initially, weekly during first 13 weeks of study, monthly thereafter, and at interim evaluations. Feed consumption measured for a 7-day period once every 4 weeks.
Method of Sacrifice		
Anesthetization and exsanguination	Same as 14-day studies	Carbon dioxide asphyxiation
Necropsy		
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, left testicle, and thymus.	Same as 14-day studies	Necropsy performed on all animals. Organs weighed at the interim evaluations were brain, kidneys, and liver.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of Manganese (II) Sulfate Monohydrate (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Clinical Pathology		
Blood samples were collected from the vena cava of all animals at the end of the studies. Tissue samples of livers of high-dose and control animals were collected. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, and leukocyte count and differential ***Tissue metal concentration analyses:*** manganese concentration	Blood was collected from the vena cava of all animals at the end of the studies. ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, and leukocyte count and differential	Blood was collected at the 9- and 15-month interim evaluations for hematology and clinical chemistry determinations. Samples of blood plasma (rats), kidneys, livers, and pancreas were collected at the 9- and 15-month evaluations for tissue metal concentration analyses. ***Hematology:*** Erythrocytes, hemoglobin, hematocrit, platelets, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, reticulocytes, nucleated erythrocytes, and leukocyte count and differential ***Clinical chemistry:*** alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, blood urea nitrogen, and creatinine ***Tissue metal concentration analyses:*** manganese, iron, copper, and zinc concentrations
Histopathology		
None	Complete histopathologic examinations were performed on all control and high-dose animals. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, blood, bone marrow (sternum), brain, cecum (rats), colon, duodenum, esophagus, gallbladder (mice), heart, kidney, liver, lung, mammary gland, mandibular lymph node, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland (rats), prostate gland, salivary gland, spleen, stomach, testes/epididymis, thyroid gland, trachea, thymus, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all 0 and 15,000 ppm animals at the 9- and 15-month interim evaluations and gross lesions examined for the 1,500 and 5,000 ppm groups. Complete histopathologic examinations were performed on all animals at the end of the studies and on all animals that died or were killed moribund during the studies. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, bone, bone marrow, brain, cecum, colon and rectum, esophagus, gallbladder (mice), heart, kidney, liver, lung, mandibular and mesenteric lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, skin, small intestine, spleen, stomach (forestomach and glandular), testes/epididymis, thymus, thyroid gland, trachea, uterus, and urinary bladder.

RESULTS

RATS

14-DAY STUDY

All rats survived to the end of the study (Table 2). The mean body weight gain of the male 50,000 ppm group at the end of the 14-day study was 57% less than that of the control group, and the final mean body weight of this group was 13% lower than that of the controls. The mean body weight gain of 50,000 ppm females was 20% less than that of the controls and the final mean body weight was 7% lower than that of the controls. Males and females in each exposure group consumed approximately equal amounts of manganese (II) sulfate monohydrate per body weight (25 to 370 mg/kg). During the first week, feed consumption by 50,000 ppm males was 19% lower than controls, whereas that by 50,000 ppm females was 15% lower. During the second week, however, feed consumption by both male and female 50,000 ppm groups was similar to that by controls.

Males exposed to 50,000 ppm and all exposed groups of females exhibited diarrhea during the second week. In the hematology evaluation, the total leukocyte and neutrophil counts were significantly increased in 50,000 ppm groups, particularly males (Table G1). Other slight changes in hematology parameters were not considered related to chemical ingestion. At necropsy, the absolute and relative liver weights of 50,000 ppm male rats were significantly lower than those of the controls (Table F1). Manganese concentrations in the livers of 50,000 ppm males and females were more than twice those of controls (males: control, 2.80 μg/g; 50,000 ppm, 5.92 μg/g; females: 2.40 μg/g, 6.82 μg/g).

TABLE 2
Survival, Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of Manganese (II) Sulfate Monohydrate

Concentration (ppm)	Survival[a]	Mean Body Weight and Weight Changes[b] (g) Initial	Final	Change	Relative Final Weight Feed to Controls (%)	Consumption[c] Week 1	Week 2
Male							
0	5/5	183 ± 14	241 ± 12	58 ± 2		17.2	17.2
3,130	5/5	176 ± 6	235 ± 5	59 ± 3	98	16.6	17.2
6,250	5/5	182 ± 15	242 ± 13	60 ± 3	101	16.7	17.7
12,500	5/5	176 ± 7	235 ± 6	58 ± 3	98	16.7	17.7
25,000	5/5	186 ± 7	243 ± 6	57 ± 1	101	17.0	18.1
50,000	5/5	185 ± 5	210 ± 6*	25 ± 2**	87	13.9	16.8
Female							
0	5/5	140 ± 3	165 ± 4	25 ± 2		12.2	11.4
3,130	5/5	144 ± 5	171 ± 5	27 ± 3	104	14.2	11.8
6,250	5/5	134 ± 4	157 ± 3	23 ± 2	95	11.8	11.0
12,500	5/5	136 ± 5	163 ± 6	27 ± 1	99	13.2	11.9
25,000	5/5	139 ± 5	166 ± 4	27 ± 1	101	13.3	12.0
50,000	5/5	134 ± 5	153 ± 5	20 ± 1	93	10.4	12.1

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
** $P \leq 0.01$
[a] Number of animals surviving at 14 days/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

13-WEEK STUDY

Because of the decreased mean body weight gains in the 50,000 ppm male and female rat groups in the 14-day study, 25,000 ppm was selected as the high dose for males and females in the 13-week study. No rats died during the study, but the mean body weight gain in males receiving 3,130 ppm was marginally lower than that of the controls and was significantly lower in the three highest female dose groups than the controls (Table 3). Final mean body weights of all exposed animals were within 5% of those of the controls. Feed consumption by exposed rats was similar to that by the controls (Table 3). Mean daily ingestion of manganese (II) sulfate monohydrate ranged from 110 to 1,700 mg/kg body weight in males and 115 to 2,000 mg/kg in females. Females ingested an average of 20% more manganese (II) sulfate monohydrate than males in the corresponding exposure groups.

Absolute and relative liver weights of all exposed males and of the female 25,000 ppm group were significantly lower than those of the controls (Table F2). The absolute and relative lung weights of all exposed females were also significantly lower than those of controls. No other biologically significant organ weight differences were observed between exposed and control animals. Although the total leukocyte counts were similar in exposed and control males, neutrophil counts were significantly higher in all exposed male groups, whereas lymphocyte counts were significantly lower in the 6,250, 12,500, and 25,000 ppm groups (Table G2). In contrast, the total leukocyte counts of 6,250, 12,500, and 25,000 ppm females were significantly lower, primarily because of lower lymphocyte counts. A marginal but significant increase in percent hematocrit and erythrocyte counts occurred in males exposed to 6,250, 12,500, or 25,000 ppm. The relationship between these differences and the ingestion of manganese (II) sulfate monohydrate is not clear. No clinical or histopathologic findings were attributed to the administration of manganese (II) sulfate monohydrate.

TABLE 3
Survival, Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate

Concentration (ppm)	Survival[a]	Mean Body Weight and Weight Changes[b] Initial	Final	Change	Final Weight Relative Feed to Controls (%)	Consumption[c] Week 1	Week 13
Male							
0	10/10	136 ± 5	291 ± 4	155 ± 4		14.9	13.1
1,600	10/10	142 ± 4	294 ± 5	152 ± 4	101	14.5	13.5
3,130	10/10	149 ± 3	291 ± 4	141 ± 4	100	14.8	13.6
6,250	10/10	148 ± 2	294 ± 3	146 ± 3	101	15.0	9.6
12,500	10/10	150 ± 11	290 ± 6	140 ± 11	99	14.9	14.9
25,000	10/10	140 ± 4	284 ± 6	144 ± 4	97	14.1	14.4
Female							
0	10/10	99 ± 1	184 ± 2	84 ± 2		10.7	9.2
1,600	10/10	103 ± 1	181 ± 2	79 ± 2	99	10.8	9.3
3,130	10/10	96 ± 1	175 ± 2*	80 ± 3	95	10.9	9.2
6,250	10/10	101 ± 1	176 ± 2*	75 ± 1**	96	10.7	14.3
12,500	10/10	106 ± 1**	178 ± 1*	73 ± 2**	97	10.7	10.5
25,000	10/10	104 ± 1**	174 ± 3**	70 ± 2**	95	12.1	10.3

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
** $P \leq 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.

Dose Selection Rationale: Based on decreases in body weight gain and the lower absolute and relative liver weights in the 25,000 ppm groups in the 13-week study, doses of 0, 1,500, 5,000, and 15,000 ppm were selected for the 2-year study in rats.

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats administered manganese (II) sulfate monohydrate in feed for 2 years are presented in Table 4 and in Kaplan-Meier survival curves (Figure 1). Survival of 15,000 ppm male rats was significantly lower than that of the controls; survival of 1,500 and 5,000 ppm males and all exposed groups of females was similar to that of controls. The significant reduction in survival of 15,000 ppm males was attributed to increased severity of nephropathy and renal failure. The decreased survival did not occur until approximately week 93 of the study (Figure 1).

TABLE 4
Survival of Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	Control	1,500 ppm	5,000 ppm	15,000 ppm
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	8	10	10	10
15-Month interim evaluation[a]	10	9	9	8
Moribund	21	24	24	38
Natural deaths	6	10	5	7
Animals surviving to study termination	25	17	22[b]	7
Percent probability of survival at end of study[c]	49	34	43	14
Mean survival (days)[d]	581	573	579	571
Survival analyses[e]	P=0.004	P=0.381	P=0.872	P=0.006
Female				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	10	10	9	10
Accidental deaths[a]	0	0	1	0
Moribund	6	11	6	11
Natural deaths	7	2	2	1
Missexed[a]	0	0	0	2
Animals surviving to study termination	37	37	42	36
Percent probability of survival at end of study	74	74	85	75
Mean survival (days)	608	594	596	607
Survival analyses	P=0.914N	P=0.986	P=0.378N	P=0.984N

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

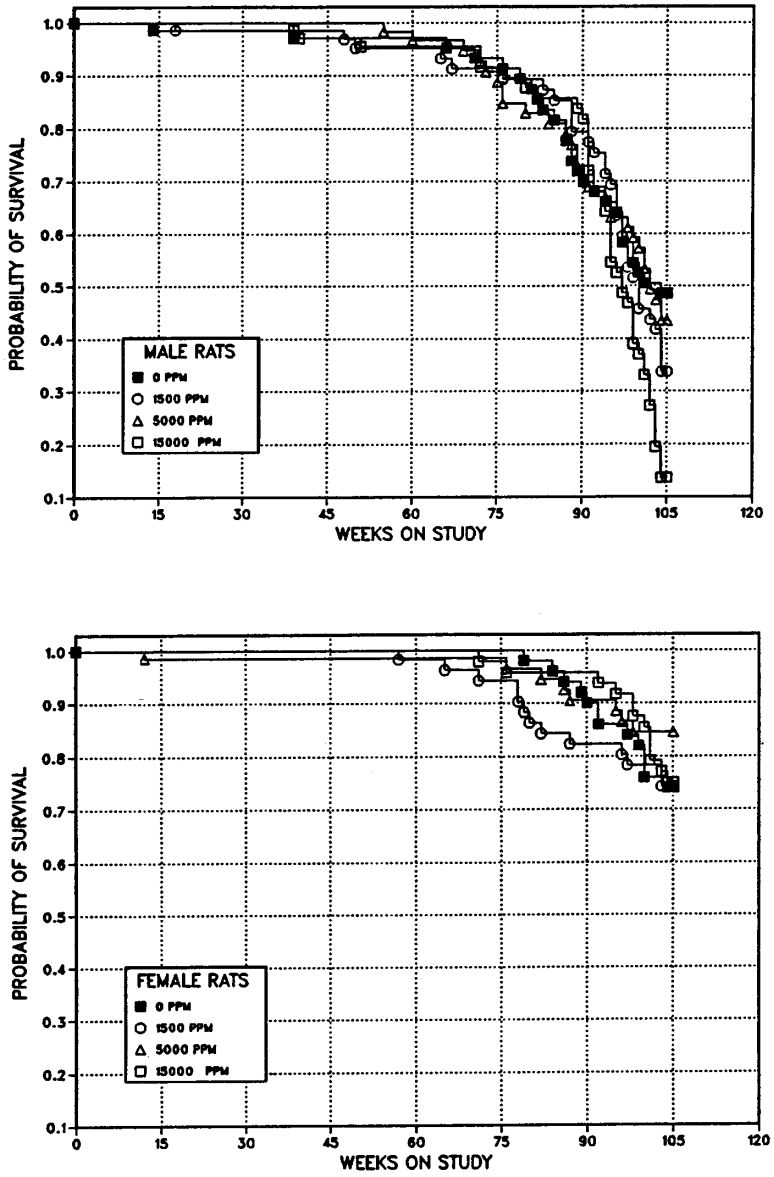

FIGURE 1
Kaplan-Meier Survival Curves for Male and Female F344/N Rats Administered Manganese (II) Sulfate Monohydrate in Feed for 2 Years

Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of 1,500 and 5,000 ppm male rats exposed to manganese (II) sulfate monohydrate were similar to those of controls throughout the 2-year study (Table 5 and Figure 2). The mean body weights of 15,000 ppm male rats were within 5% of that of controls until week 89. From week 89, the mean body weights ranged from 8% to 13% lower than that of controls; at the end of the 2-year study, the final mean body weight of 15,000 ppm males was 10% lower than that of controls. Mean body weights of exposed females were similar to that of controls throughout the study (Table 6). Feed consumption by exposed groups was similar to that by control groups (Tables J1 and J2). Rats exposed to 1,500, 5,000, or 15,000 ppm manganese (II) sulfate monohydrate received approximate daily doses of 60, 200, or 615 mg/kg body weight (males) or 70, 230, or 715 mg/kg (females). No clinical findings were chemical related.

Hematology, Clinical Chemistry, and Tissue Metal Concentration Analyses

Values for hematology and clinical chemistry parameters were generally similar among exposed and control groups at the 9- and 15-month interim evaluations (Tables G3 and G4). Slight differences in some parameters between exposed and control groups were not considered related to the ingestion of manganese (II) sulfate monohydrate. At both the 9- and 15-month interim evaluations, the manganese levels in the liver of 5,000 and 15,000 ppm males and females were significantly greater than those in controls. The hepatic iron concentrations for these exposure groups were lower than for controls (Tables H1 and H2). The concentrations of manganese in the brain, kidney, and pancreas of exposed and control rats were variable; 15,000 ppm males had a significantly higher concentration of manganese in the brain and kidney at the 9-month interim evaluation and in the brain, kidney, and pancreas at the 15-month interim evaluation. Copper levels in the kidney of 15,000 ppm males at 9 months and in 15,000 ppm females at 9 and 15 months were significantly greater than those of the controls.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions in the pancreas, kidney, and adrenal gland. No chemical-related lesions were observed at the 9- or 15-month interim evaluations. Summaries of the incidences of neoplastic 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 for male rats and B for female rats.

Pancreas: Hyperplasia or adenoma of the pancreatic islets occurred in a few males in each of the exposure groups but not in the control group (hyperplasia: control, 0/52; 1,500 ppm, 2/50; 5,000 ppm, 2/51; 15,000 ppm, 3/51; adenoma: 0/52, 3/50, 4/51, 3/51; Tables A5 and A1). In addition, a carcinoma of the pancreatic islets was found in one 15,000 ppm male. However, neither the trend test nor pairwise comparisons were significant (Table A3), and the incidences in each of the dose groups were within the range of NTP historical control groups (adenoma, 0% to 12%; carcinoma, 0% to 6%; Table A4a).

Kidney: At the 9- and 15-month interim evaluations, the absolute kidney weights of exposed rats were similar to those of the controls (Tables F3 and F4). Chronic nephropathy occurred in all male rats examined at both interim evaluations and most of the control and exposed males at the end of the study (Tables 7 and A5). The average severity of nephropathy was slightly greater in the high-dose group, but the difference was not statistically significant. Because of the subjective nature of the severity grading, an additional evaluation of the kidney of high-dose and control male rats was performed without knowledge of the previous diagnoses. The result of the additional evaluation confirmed the presence of a marginally increased severity of nephropathy in the high-dose group, and the difference was significant (P=0.04) by a two-sided MannWhitney U test. The severity of nephropathy varied from minimal to marked. Minimal nephropathy was characterized by a few sparsely scattered cortical foci of regenerating tubules with increased epithelial cytoplasmic basophilia and slightly thickened glomerular basement membranes. Nephropathy of mild severity had similar morphologic features, but these features occurred with greater frequency. Also present were occasional dilated tubules filled with homogenous hyaline material and lined by flattened epithelial cells. Nephropathy of moderate to marked severity had similar but more severe and extensive tubule

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Weeks on Study	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	126	70	124	98	70	126	100	70	123	98	70
2	167	70	166	100	70	167	101	70	164	98	70
3	201	70	197	98	70	202	101	70	193	96	70
4	227	70	220	97	70	228	100	70	220	97	70
5	247	70	244	98	70	251	101	70	244	99	70
6	272	70	268	98	70	274	101	70	268	98	70
7	283	70	280	99	70	287	102	70	280	99	70
8	297	70	295	99	70	303	102	70	293	99	70
9	314	70	307	98	70	313	100	70	306	98	70
10	327	70	318	97	70	328	100	70	321	98	70
11	334	70	327	98	70	334	100	70	324	97	70
12	343	70	335	98	70	343	100	70	335	98	70
13	353	70	347	98	70	351	99	70	341	97	70
18	386	69	375	97	70	383	99	70	376	97	70
21	399	69	394	99	69	394	99	70	386	97	70
25	415	69	408	98	69	411	99	70	399	96	70
28	431	69	423	98	69	425	98	70	416	96	70
32	447	69	440	98	69	441	99	70	429	96	70
36	462	69	455	99	69	453	98	70	442	96	70
40[a]	460	60	453	98	60	452	98	60	441	96	58
44	472	60	450	95	60	451	96	60	441	93	58
48	480	60	474	99	58	476	99	60	466	97	58
53	484	60	479	99	57	479	99	60	471	97	57
57	496	60	487	98	57	487	98	59	482	97	57
61	497	60	485	98	57	490	99	58	481	97	57
65[a]	505	50	488	97	48	493	98	49	488	97	49
69	509	49	487	96	46	491	97	49	486	95	49
73	510	48	493	97	46	497	97	47	493	97	47
77	509	47	490	96	45	496	98	43	490	96	46
81	498	46	479	96	45	484	97	42	477	96	45
85	492	43	479	97	44	484	99	41	478	97	44
89	486	38	469	97	40	469	97	39	449	92	43
93	472	35	451	96	38	460	97	35	432	91	35
97	449	31	426	95	32	443	99	32	409	91	26
101	433	26	431	100	23	423	98	28	378	87	18
104	402	26	402	100	20	393	98	24	360	90	10
Mean for weeks											
1-13	269		264	98		270	100		262	97	
14-52	439		430	98		432	98		422	96	
53-104	482		468	97		471	98		455	94	

[a] Interim evaluations occurred during weeks 39 and 65.

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Weeks on Study	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	104	70	103	100	70	104	100	70	103	99	70
2	127	70	128	101	70	128	101	70	126	99	69
3	143	70	143	100	70	143	100	70	142	99	69
4	154	70	154	100	70	153	99	70	151	98	68
5	161	70	164	102	70	160	99	70	160	99	68
6	170	70	173	102	70	170	100	70	168	99	68
7	174	70	179	103	70	176	101	70	175	101	68
8	181	70	184	102	70	181	100	69	181	100	68
9	186	70	190	102	70	186	100	69	186	100	68
10	190	70	194	102	70	190	100	69	190	100	68
11	191	70	195	102	70	192	100	69	191	100	68
12	196	70	198	101	70	196	100	68	195	100	68
13	199	70	201	101	70	199	100	68	198	100	68
18	205	70	208	101	70	206	100	68	205	100	68
21	210	70	213	101	70	211	100	68	211	100	68
25	217	70	221	102	70	218	100	68	217	100	68
28	225	70	225	100	70	222	99	68	223	99	68
32	232	70	236	102	70	231	100	68	231	100	68
36	237	70	244	103	70	240	101	68	237	100	68
40[a]	241	60	245	102	60	240	101	58	243	101	58
44	249	60	257	103	60	251	101	58	251	101	58
48	258	60	260	101	60	261	101	58	266	103	58
53	272	60	277	102	60	270	99	58	277	102	58
57	277	60	287	104	60	279	101	58	287	104	58
61	286	60	294	103	59	287	101	58	295	103	58
65[a]	296	50	305	103	48	298	101	49	303	103	48
69	305	50	313	103	48	306	101	49	312	102	48
73	311	50	320	103	47	316	101	49	318	102	47
77	321	50	327	102	47	328	102	48	329	103	46
81	327	49	332	102	43	333	102	48	335	103	46
85	335	48	339	101	42	340	102	47	342	102	46
89	336	47	346	103	41	346	103	45	346	103	46
93	340	43	342	101	41	345	102	45	345	102	45
97	334	43	335	100	39	341	102	43	337	101	44
101	336	38	330	98	39	337	100	42	333	99	38
104	327	38	326	100	37	336	103	42	336	103	36
Mean for weeks											
1-13	167		170	102		168	101		167	100	
14-52	230		234	102		231	100		232	101	
53-104	315		320	102		319	101		321	102	

[a] Interim evaluations occurred during weeks 39 and 65.

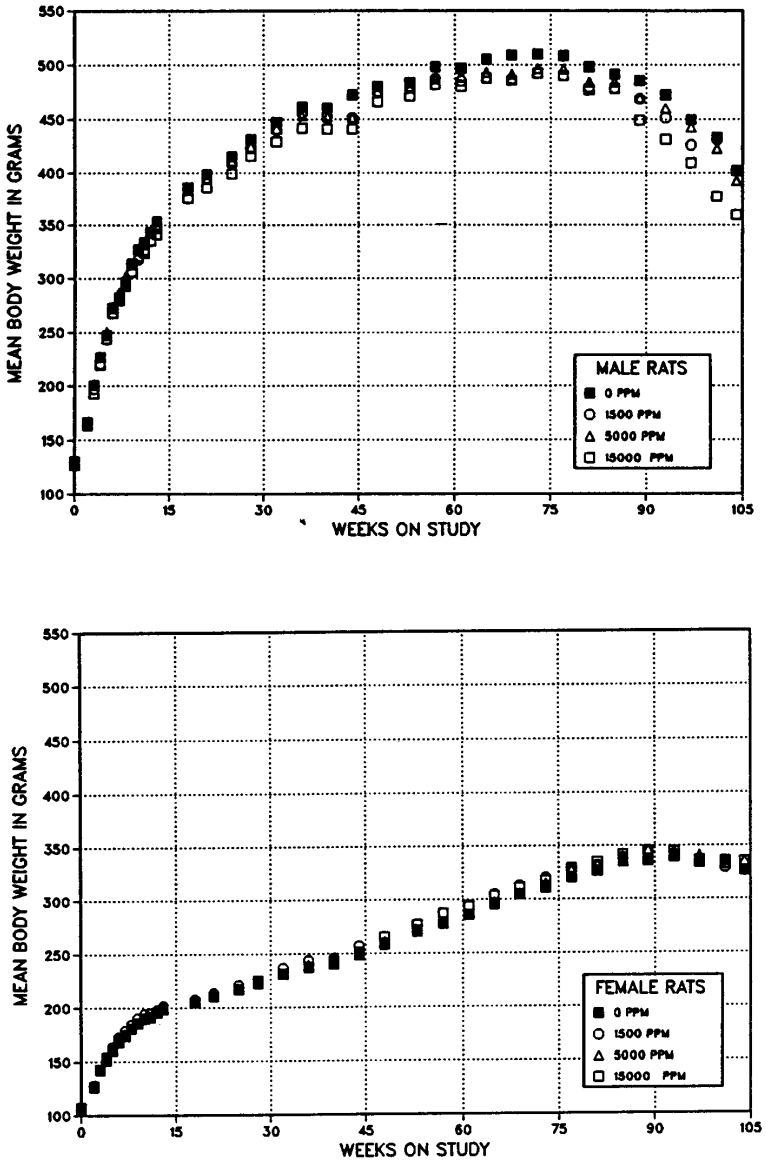

FIGURE 2
Growth Curves for Male and Female F344/N Rats Administered Manganese (II) Sulfate Monohydrate in Feed for 2 Years

lesions. In addition, variable interstitial fibrosis and mineralization with mononuclear leukocyte infiltration, variable tubule loss and atrophy, and degenerative glomerular changes occurred. In the most severe cases, cystic tubules lined by cuboidal or attenuated epithelial cells were present.

The incidences of several lesions commonly associated with advanced nephropathy and renal failure were significantly increased in 15,000 ppm male rats. These lesions included mineralization of blood vessels (4/52, 10/51, 6/51, 17/52), mineralization of the glandular stomach (8/52, 13/51, 9/51, 23/52), fibrous osteodystrophy of the femur (12/52, 14/51, 12/51, 24/52), and parathyroid gland hyperplasia (14/51, 14/46, 12/49, 23/50) (Table A5).

Adrenal Gland: In females, medullary hyperplasia occurred with a significant negative trend and a significantly decreased incidence in the 15,000 ppm group (control 12/50, 1,500 ppm 11/50, 5,000 ppm 6/51, and 15,000 ppm 1/48; Table B4). Benign pheochromocytomas of the adrenal medulla in males occurred with a significant negative trend, but the decreases were not significant by pairwise comparison (14/52, 17/51, 14/51, and 6/52; Table A3); the incidence of medullary hyperplasia in exposed males was similar to that of the controls (Table A5).

TABLE 7
Incidence and Severity of Nephropathy of Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Dose (ppm)	0	1,500	5,000	15,000
Males				
9-Month Interim Evaluation				
Kidney[a]	8	10	10	10
Nephropathy[b]	8 (1.3)[c]	10 (1.1)	10 (1.1)	10 (1.3)
15-Month Interim Evaluation				
Kidney	10	9	9	8
Nephropathy	10 (1.6)	9 (1.9)	9 (1.9)	8 (2.0)
2-Year Study				
Kidney	52	50	51	52
Nephropathy (initial evaluation)	50 (2.9)	49 (3.0)	51 (3.0)	50 (3.2)
Nephropathy (additional evaluation)	52 (2.8)	–	–	51 (3.1)*
Females				
2-Year Study				
Kidney	50	50	51	48
Nephropathy	48 (1.8)	50 (1.5)	49 (1.7)	48 (1.9)

* Significantly different ($P \leq 0.05$) from the control group by two-sided Mann-Whitney U test
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in all animals (0=normal; 1=minimal; 2=mild; 3=moderate; 4=marked)

MICE

14-DAY STUDY

One female mouse in the 25,000 ppm group died of unknown causes on day 1; all other mice survived to the end of the study (Table 8). No significant evidence of toxicity was observed except possible body weight effects in both sexes. However, no conclusions can be made regarding the body weight data because of poor randomization of animals at study initiation. No organ weight differences were attributed to manganese (II) sulfate monohydrate exposure (Table F5). Absolute or relative organ weight differences in some of the exposure groups were probably related to body weight differences between exposed and control groups. No chemical-related differences in hematology parameters were observed (Table G5). Manganese concentrations in the livers of 50,000 ppm mice were 8 to 15 times higher than those found in controls (males: control, 0.966 μg/g; 50,000 ppm, 8.020 µg/g; females: 0.708 μg/g; 10.300 μg/g).

TABLE 8
Survival, Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of Manganese (II) Sulfate Monohydrate

Concentration (ppm)	Survival[a]	Mean Body Weight and Weight Changes[b] (g) Initial	Final	Change	Final Weight Relative Feed to Controls (%)	Consumption[c] Week 1	Week 2
Male							
0	5/5	21.4 ± 0.6	25.6 ± 1.2	4.2 ± 0.8		4.2	4.2
3,130	5/5	23.8 ± 0.4*	26.8 ± 0.7	3.0 ± 0.5	105	2.8	3.2
6,250	5/5	24.4 ± 0.5**	26.0 ± 1.0	1.6 ± 0.5**	102	3.0	3.5
12,500	5/5	24.6 ± 0.7**	24.0 ± 0.7	−0.6 ± 0.5**	94	3.7	4.3
25,000	5/5	24.8 ± 0.4**	24.4 ± 0.2	−0.4 ± 0.2**	95	5.1	4.6
50,000	5/5	19.2 ± 0.4*	21.8 ± 0.7*	2.6 ± 0.5**	85	3.2	4.9
Female							
0	5/5	15.6 ± 0.6	21.0 ± 1.0	5.4 ± 0.8		3.3	4.2
3,130	5/5	18.4 ± 0.2**	18.0 ± 0.3**	−0.4 ± 0.2**	86	3.8	4.8
6,250	5/5	17.8 ± 0.2**	17.2 ± 0.4**	−0.6 ± 0.4**	82	4.1	4.3
12,500	5/5	18.6 ± 0.7**	16.8 ± 0.6**	−1.8 ± 0.4**	80	4.1	5.2
25,000	4/5[d]		18.2 ± 0.4**	17.0 ± 0.4**	−1.3 ± 0.3**	81	4.8
6.0							
50,000	5/5	18.6 ± 0.4**	15.2 ± 0.5**	−3.4 ± 0.2**	72	3.5	3.9

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test.
** $P \leq 0.01$
[a] Number of animals surviving at 14 days/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.
[d] Day of death: 1

13-WEEK STUDY

The doses selected for the 13-week study were the same as those used in the 14-day study. One control male mouse and one female mouse receiving 3,130 ppm died of unknown causes during this study (Table 9). Mean body weight gains of all exposed males were significantly lower than that of the control group, and the final mean body weight of the 50,000 ppm group was 13% lower than that of the controls. The mean body weight gain of 50,000 ppm females was significantly lower than that of the controls. Feed consumption by exposed male and female mice was similar to that by the controls (Table 9). Mean daily ingestion of manganese (II) sulfate monohydrate ranged from 330 to 7,400 mg/kg body weight in males and 390 to 6,900 ppm in females. The absolute and relative liver weights of 50,000 ppm male mice were significantly lower than those of the controls (Table F6); absolute and relative liver weights of females were similar to those of the controls. The percent hematocrit, hemoglobin concentrations, and mean erythrocyte volumes of 50,000 ppm male and female mice were significantly lower than those of the controls (Table G6). These findings suggest microcytic anemia and may be related to a sequestration or deficiency of iron. Although the total leukocyte counts in the two highest male exposure groups were significantly lower than that in the control group, this may not be related to manganese (II) sulfate monohydrate ingestion. A few mice in the male and female exposure groups exhibited fight wounds. Three 50,000 ppm males had mild epithelial hyperplasia and hyperkeratosis of the forestomach.

Dose Selection Rationale: The doses selected for the 2-year study in mice were 0, 1,500, 5,000, and 15,000 ppm. These doses were based on the significantly lower mean body weight gains of all exposed males and 50,000 ppm females and the significantly lower absolute and relative liver weights of 50,000 ppm males in the 13-week study.

TABLE 9
Survival, Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate

Concentration (ppm)	Survival[a]	Mean Body Weight and Weight Changes[b] Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	9/10[d]	25.0 ± 0.5	31.4 ± 0.6	6.6 ± 0.5		3.4	3.0
3,130	10/10	25.7 ± 0.3	30.5 ± 0.5	4.8 ± 0.4**	97	3.0	3.0
6,250	10/10	26.3 ± 0.2*	31.0 ± 0.3	4.7 ± 0.4**	99	3.4	3.3
12,500	10/10	26.0 ± 0.3	30.9 ± 0.4	4.9 ± 0.4**	98	3.4	3.8
25,000	10/10	25.9 ± 0.2	30.6 ± 0.5	4.7 ± 0.5**	97	2.6	3.3
50,000	10/10	25.1 ± 0.4	27.4 ± 0.3**	2.3 ± 0.4**	87	3.0	4.7
Female							
0	10/10	20.0 ± 0.2	24.2 ± 0.3	4.2 ± 0.3		2.4	2.3
3,130	9/10[e]	20.0 ± 0.3	24.2 ± 0.5	4.1 ± 0.3	100	3.3	2.4
6,250	10/10	20.5 ± 0.2	24.3 ± 0.3	3.8 ± 0.3	100	2.8	2.2
12,500	10/10	21.0 ± 0.3	24.5 ± 0.3	3.5 ± 0.3	101	2.7	3.0
25,000	10/10	20.3 ± 0.3	24.2 ± 0.4	3.9 ± 0.4	100	3.1	3.4
50,000	10/10	20.1 ± 0.2	22.8 ± 0.3**	2.7 ± 0.2**	94	2.8	3.0

* Significantly different ($P \le 0.05$) from the control group by Williams' or Dunnett's test.
** $P \le 0.01$
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams per animal per day.
[d] Week of death: 11
[e] Week of death: 6

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice administered manganese (II) sulfate monohydrate in feed for 2 years are presented in Table 10 and in Kaplan-Meier survival curves (Figure 3). Survival of exposed males and females was similar to that of the control groups.

Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of exposed males were similar to those of the control group (Table 11 and Figure 4). After week 37, mean body weights of all exposed groups of females were lower than that of the controls (Table 12); the final mean body weights for the 1,500, 5,000, and 15,000 ppm groups were 6%, 9%, and 13% lower than that of the control group. Feed consumption by exposed male and female mice was similar to that of the control groups (Tables J3 and J4). Mice exposed to 1,500, 5,000, or 15,000 ppm manganese (II) sulfate monohydrate received approximate daily doses of 160, 540, or 1,800 mg/kg body weight (males) or 200, 700, or 2,250 mg/kg body weight (females). No clinical findings were attributed to the administration of manganese (II) sulfate monohydrate.

TABLE 10
Survival of Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	Control	1,500 ppm	5,000 ppm	15,000 ppm
Male				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	9
15-Month interim evaluation[a]	10	10	9	10
Accidental deaths[a]	0	0	0	1
Moribund	2	3	2	1
Natural deaths	2	3	3	3
Animals surviving to study termination	46[b]	44[b]	46	46
Percent probability of survival at end of study[c]	92	88	91	93
Mean survival (days)[d]	620	619	615	615
Survival analyses[e]	P=0.920N	P=0.708	P=0.992	P=0.748
Female				
Animals initially in study	70	70	70	70
9-Month interim evaluation[a]	10	10	10	10
15-Month interim evaluation[a]	9	10	9	9
Accidental deaths[a]	1	0	0	0
Moribund	6	4	6	4
Natural deaths	2	0	6	5
Missing[a]	0	0	1	0
Animals surviving to study termination	42	46	38	42
Percent probability of survival at end of study	85	92	77	83
Mean survival (days)	605	623	594	614
Survival analyses	P=0.563	P=0.318N	P=0.456	P=0.961

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

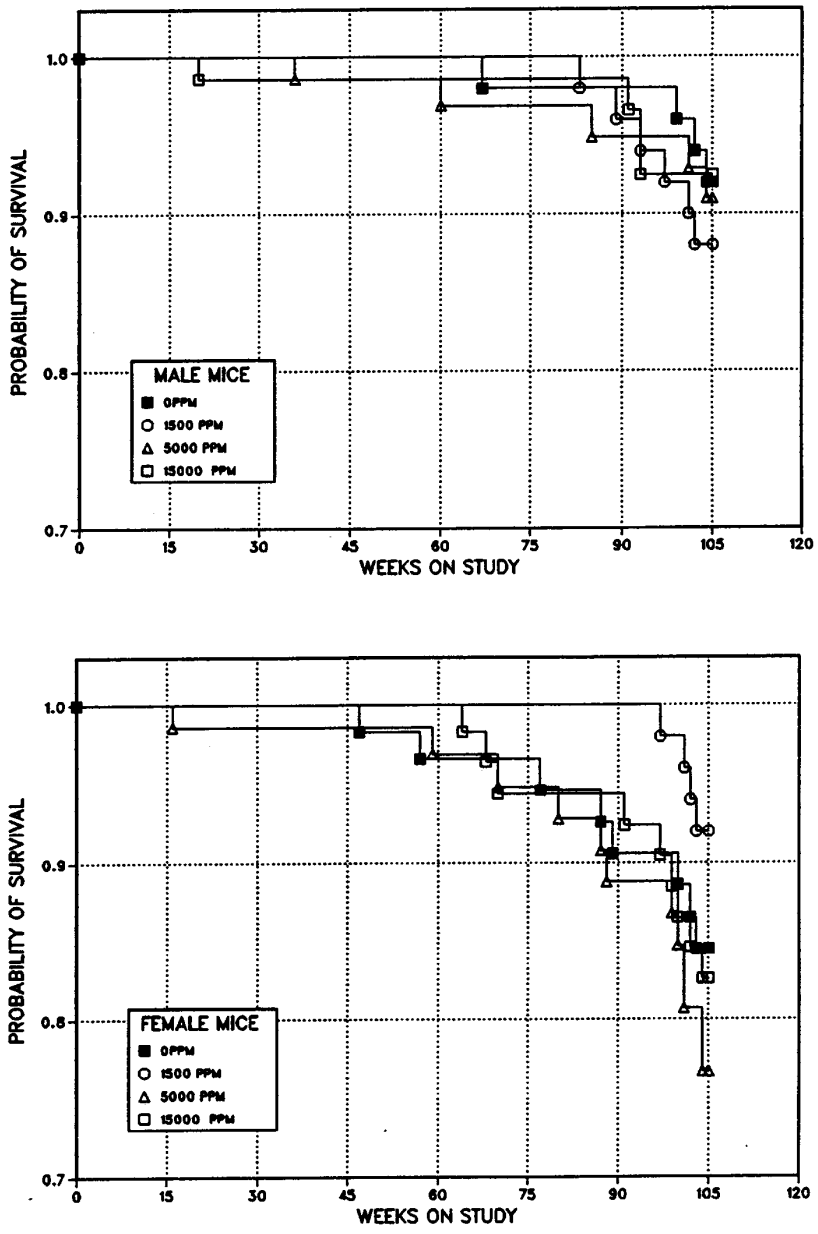

FIGURE 3
Kaplan-Meier Survival Curves for Male and Female B6C3F$_1$ Mice Administered Manganese (II) Sulfate Monohydrate in Feed for 2 Years

TABLE 11
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Weeks on Study	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	21.1	70	21.1	100	70	21.1	100	70	20.6	98	70
2	22.9	70	22.7	99	70	22.8	100	70	22.1	97	70
3	23.8	70	23.9	100	70	23.6	99	70	23.1	97	70
4	24.7	70	25.1	102	70	24.8	100	70	24.2	98	70
5	25.6	70	26.1	102	70	25.7	100	70	25.0	98	70
6	26.2	70	26.9	103	70	26.4	101	70	25.8	99	70
7	27.4	70	28.1	103	70	27.6	101	70	26.9	98	70
8	27.7	70	28.4	103	70	27.6	100	70	26.9	97	70
9	28.7	70	29.2	102	70	28.8	100	70	27.8	97	70
10	29.1	70	29.4	101	70	29.1	100	70	28.1	97	70
11	29.9	70	30.3	101	70	30.1	101	70	29.0	97	70
12	30.5	70	31.3	103	70	30.9	101	70	29.5	97	70
13	31.6	70	32.5	103	70	31.8	101	70	30.6	97	70
17	34.1	70	35.2	103	70	34.6	102	70	32.8	96	70
21	36.9	70	37.9	103	70	37.1	101	70	35.4	96	69
25	39.0	70	40.1	103	70	39.3	101	70	37.6	96	69
29	41.4	70	42.1	102	70	41.4	100	70	39.3	95	69
33	43.3	70	43.7	101	70	43.1	100	70	41.1	95	69
37	43.8	70	44.5	102	70	43.9	100	69	42.1	96	69
41[a]	44.5	60	45.2	102	60	44.8	101	59	43.2	97	60
45	45.4	60	46.5	102	60	46.0	101	59	44.4	98	60
49	46.8	60	48.2	103	60	47.4	101	59	45.8	98	60
54	46.7	60	48.0	103	60	47.3	101	59	46.0	99	60
57	46.0	60	47.6	103	60	46.5	101	59	45.7	99	60
61	46.6	60	48.0	103	60	47.1	101	58	46.4	100	60
65[a]	47.0	50	48.4	103	50	47.3	100	49	46.4	99	49
69	46.9	49	48.2	103	50	47.1	100	49	45.7	97	49
73	46.8	49	48.1	103	50	46.5	99	49	45.3	97	49
78	46.4	49	48.3	104	50	47.1	102	49	46.0	99	49
82	47.7	49	49.3	103	50	48.2	101	49	46.6	98	49
86	47.8	49	48.9	102	49	48.2	101	48	46.8	98	49
90	48.4	49	48.9	101	48	48.7	101	48	47.4	98	49
94	47.0	49	47.6	101	47	47.0	100	48	46.2	98	46
98	46.6	49	48.1	103	46	47.0	101	48	45.7	98	46
101	45.9	48	46.9	102	44	44.9	98	47	44.0	96	46
104	45.2	47	46.3	102	44	44.9	99	47	44.1	98	46
Mean for weeks											
1-13	26.9		27.3	102		26.9	100		26.1	97	
14-52	41.7		42.6	102		42.0	101		40.2	96	
53-104	46.8		48.0	103		47.0	100		45.9	98	

[a] Interim evaluations occurred during weeks 39 and 65.

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Weeks on Study	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.2	70	17.0	99	70	17.1	99	70	17.0	99	70
2	18.4	70	18.4	100	70	18.5	101	70	18.0	98	70
3	19.5	70	19.5	100	70	19.5	100	70	19.2	99	70
4	20.6	70	20.7	101	70	20.7	101	69	20.0	97	70
5	21.6	70	21.7	101	70	21.5	100	69	20.7	96	70
6	21.9	70	22.0	101	70	21.9	100	69	21.3	97	70
7	23.0	70	22.8	99	70	22.9	100	69	22.3	97	70
8	23.4	70	23.8	102	70	23.6	101	69	22.9	98	70
9	24.3	70	24.3	100	70	24.3	100	69	23.9	98	70
10	24.5	70	24.4	100	70	24.4	100	69	23.8	97	70
11	25.1	70	25.1	100	70	25.1	100	69	24.6	98	70
12	25.6	70	25.6	100	70	25.7	100	69	25.2	98	70
13	25.6	70	26.2	102	70	26.3	103	69	25.5	100	70
17	28.1	70	28.8	103	70	28.6	102	68	27.7	99	70
21	30.4	70	31.4	103	70	31.5	104	68	30.5	100	70
25	33.0	70	33.7	102	70	33.9	103	68	32.8	99	70
29	36.0	70	35.7	99	70	36.0	100	68	34.5	96	70
33	38.5	70	38.3	100	70	38.2	99	68	37.0	96	70
37	40.3	70	39.7	99	70	39.3	98	68	37.9	94	70
41[a]	41.9	59	41.6	99	60	40.9	98	58	39.0	93	60
45	43.8	59	43.6	100	60	42.7	98	58	41.6	95	60
49	46.3	58	46.6	101	60	45.4	98	58	43.6	94	60
54	47.6	58	47.0	99	60	45.8	96	58	43.8	92	60
57	47.6	57	47.4	100	60	46.0	97	58	43.9	92	60
61	48.6	57	48.4	100	60	46.6	96	57	45.0	93	60
65[a]	49.7	48	48.6	98	50	47.0	95	48	45.3	91	50
69	49.8	48	49.5	99	50	47.8	96	48	45.6	92	49
73	51.0	48	50.7	99	50	48.1	94	47	46.3	91	48
78	50.6	47	50.5	100	50	48.4	96	47	46.3	92	48
82	52.7	47	51.6	98	50	50.1	95	46	47.9	91	48
86	53.1	47	52.0	98	50	50.0	94	46	47.8	90	48
90	53.5	45	51.8	97	50	50.8	95	44	48.3	90	48
94	53.8	45	51.0	95	50	50.5	94	44	47.7	89	47
98	52.4	45	49.7	95	49	48.6	93	44	46.2	88	46
102	51.6	43	48.4	94	48	47.2	92	40	44.4	86	44
104	50.8	42	47.8	94	46	46.2	91	40	44.3	87	43
Mean for weeks											
1-13	22.4		22.4	100		22.4	100		21.9	98	
14-52	37.6		37.7	100		37.4	99		36.1	96	
53-104	50.9		49.6	97		48.1	94		45.9	90	

[a] Interim evaluations occurred during weeks 39 and 65.

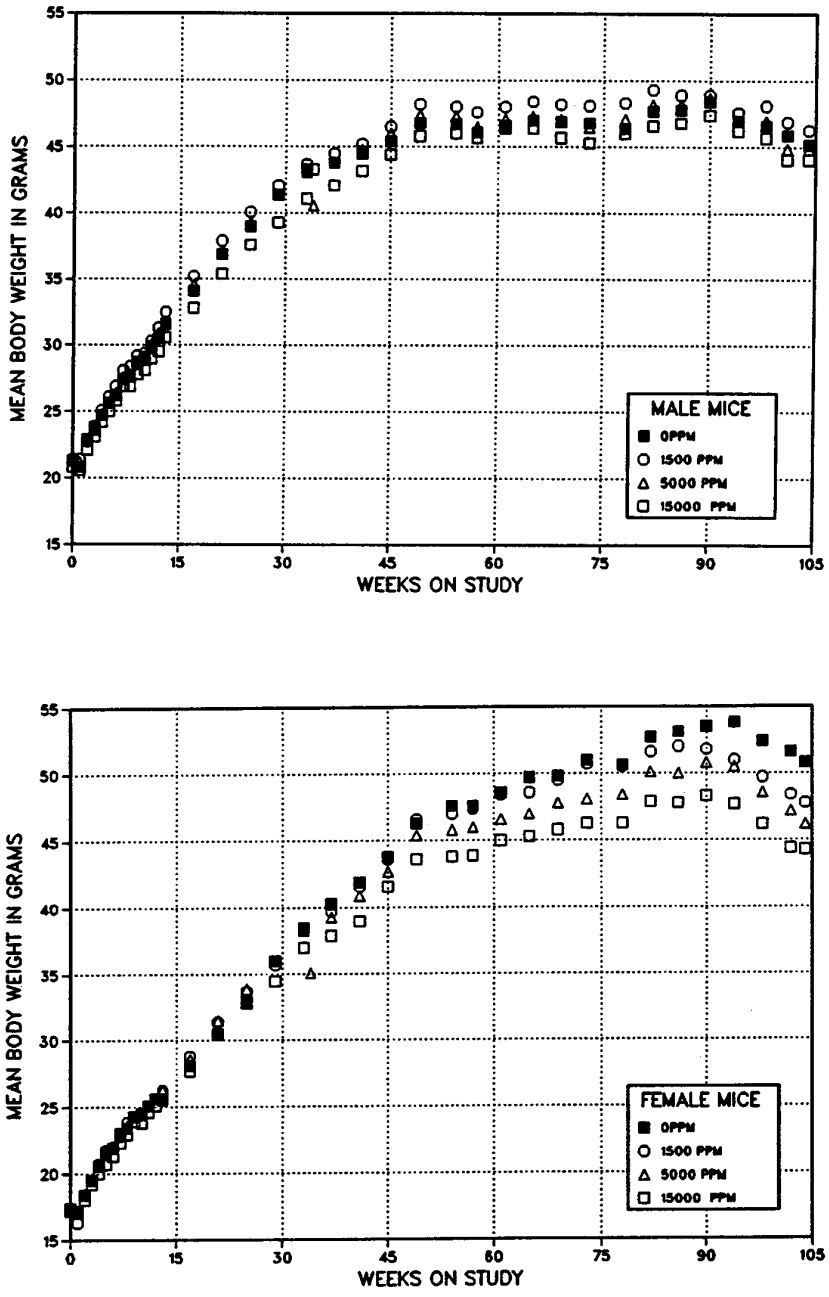

FIGURE 4
Growth Curves for Male and Female B6C3F$_1$ Mice Administered Manganese (II) Sulfate Monohydrate in Feed for 2 Years

Hematology, Clinical Chemistry, and Tissue Metal Concentration Analyses

Percent hematocrit, hemoglobin concentrations, and erythrocyte counts in 15,000 ppm male mice at the 15-month interim evaluation were greater than those of the controls. These slight increases are not consistent with the findings in the 13-week study and their significance is uncertain. No other notable differences were observed in the hematology or clinical chemistry parameters (Tables G7 and G8). At the 9- and 15-month interim evaluations, tissue concentrations of manganese were significantly elevated in the livers of the 5,000 and 15,000 ppm groups. Hepatic iron levels were significantly lower in exposed females at the 9- and 15-month interim evaluations and in 5,000 and 15,000 males at the 15-month interim evaluation. Tissue concentrations of manganese in the brain (except 1,500 and 5,000 ppm females at 15 months), kidney, and pancreas (except 1,500 males at 9 months and 1,500 ppm females at 15 months) of exposed groups were significantly greater those of controls (Tables H3 and H4).

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions in the thyroid gland, forestomach, and liver. Summaries of the incidences of neoplastic and nonneoplastic lesions, individual 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 for male mice and D for female mice.

Thyroid Gland: At the 9- and 15-month interim evaluations, thyroid follicle dilatation was present in 15,000 ppm males and females but not in the controls (Table 13). At the end of the 2-year study, the incidence of follicular dilatation increased significantly in 15,000 ppm males and 5,000 and 15,000 ppm females. A significantly increased incidence of focal hyperplasia of follicular epithelium also occurred in 15,000 ppm males and in all exposed females. Follicular cell adenomas were found in three (6%) 15,000 ppm males. This rate is marginally higher than the average rate of 2% and just within the range of 0%-6% for historical control male mice (Table C4). The incidence of this neoplasm was 10% in 15,000 ppm females, which is slightly above the average of 3% and range of 0%-9% for historical control female mice (Table D4a). The incidences of adenoma in 15,000 ppm males and females were not significantly greater than those of the controls (Tables C3 and D3).

Follicular dilatation at the 9-month evaluation was characterized by a uniform increase in the follicular diameter throughout the gland. Follicular dilatation in mice at the end of the study differed from that observed in mice at the 9-month interim evaluation in that the dilated follicles were limited to the periphery of the glands. The affected follicles contained pale eosinophilic colloid and were lined by a single layer of flat to slightly cuboidal follicular epithelial cells. Follicular cell hyperplasia and adenoma constitute a morphological continuum. Follicular cell hyperplasia consisted of single or multiple collections of variably sized follicles with irregular hypertrophy and increased cellularity of the follicular epithelium (Plates 1 and 2). Minimal to mild follicular cell hyperplasia consisted of one or several follicles lined by columnar epithelium with small and infrequent papillary infoldings. Moderate to marked hyperplasia involved clusters of variably sized follicles with more prominent papillary formations. Follicular cell adenomas were generally more discrete collections of altered follicles compressing the surrounding parenchyma (Plates 3 and 4).

Forestomach: A statistically significant increased incidence of focal squamous hyperplasia of the forestomach occurred in the 15,000 ppm males and females, accompanied by ulceration/erosion and inflammation (Table 14). Hyperplasia of the squamous epithelium occurred focally at various sites of the forestomach mucosa. The lesion was characterized by broad-based areas of either proliferative epithelial thickening and hyperkeratosis or by polypoid projections of thickened epithelium protruding directly from the mucosa into the lumen of the stomach. Inflammation of the lamina propria and submucosa subjacent to the ulcerative lesions consisted of a mixture of infiltrating neutrophils and mononuclear leukocytes.

Liver: At the 9-month interim evaluation, absolute liver weights of 15,000 ppm males and of 5,000 and 15,000 ppm females were significantly lower than those of controls (Table F7). Since these groups also had lower mean body weights, and relative liver weights were similar to controls, the lower absolute

TABLE 13
Incidences of Selected Lesions of the Thyroid Gland of Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Dose (ppm)	0	1,500	5,000	15,000
Males				
9-Month Interim Evaluation				
Thyroid Gland[a]	10	0	0	9
Follicular Dilatation[b]	0	–[c]	–	6** (1.0)[d]
15-Month Interim Evaluation				
Thyroid Gland	10	2	1	10
Follicular Dilatation	0	0	0	9** (1.0)
Follicular Cell Adenoma	0	0	0	1
2-Year Study				
Thyroid Gland	50	49	51	50
Follicular Dilatation	2 (1.0)	2 (1.5)	5 (1.0)	23** (1.2)
Follicular Cell, Hyperplasia, Focal	5 (1.0)	2 (1.5)	8 (1.5)	27** (1.9)
Follicular Cell Adenoma[e]				
Overall rate[f]	0/50 (0%)	0/49 (0%)	0/51 (0%)	3/50 (6%)
Adjusted rate[g]	0.0%	0.0%	0.0%	6.5%
Terminal rate[h]	0/46 (0%)	0/44 (0%)	0/46 (0%)	3/46 (7%)
First incidence (days)	–	–	–	729 (T)
Logistic regression test[i]	P=0.015	–	–	P=0.121
Females				
9-Month Interim Evaluation				
Thyroid Gland	10	0	1	10
Follicular Dilatation	0	–	1 (1.0)	7** (1.0)
15-Month Interim Evaluation				
Thyroid Gland	9	0	2	9
Follicular Dilatation	0	–	0	5* (1.0)
2-Year Study				
Thyroid Gland	50	50	49	51
Follicular Dilatation	1 (1.0)	5 (1.0)	11** (1.4)	24** (1.2)
Follicular Cell, Hyperplasia, Diffuse	1 (1.0)	1 (1.0)	0	0
Follicular Cell, Hyperplasia, Focal	3 (2.3)	15** (1.5)	27** (1.5)	43** (2.1)
Follicular Cell Adenoma[j]				
Overall rates	2/50 (4%)	1/50 (2%)	0/49 (0%)	5/51 (10%)
Adjusted rates	4.8%	2.2%	0.0%	11.9%
Terminal rates	2/42 (5%)	1/46 (2%)	0/37 (0%)	5/42 (12%)
First incidence (days)	729 (T)	729 (T)	–	729 (T)
Logistic regression tests	P=0.037	P=0.468N	P=0.267N	P=0.216

TABLE 13
Incidences of Selected Lesions of the Thyroid Gland of Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

(T)Terminal Sacrifice
* Significantly different (P≤0.05) from the control group by the Fisher exact test (interim evaluations) or by the logistic regression test (2-year study)
** P≤0.01
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Not applicable; tissue not examined microscopically in this group
[d] Average severity grade of lesions in affected animals (1=minimal; 2=mild; 3=moderate; 4=marked)
[e] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 19/1,105 (1.7% ± 1.7%); range 0%-4%
[f] Number of neoplasm-bearing animals/number of animals microscopically examined
[g] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[h] Observed incidence at terminal kill
[i] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these neoplasms as nonfatal. A lower incidence in an exposure group is indicated by **N**.
[j] Historical incidence: 27/1,099 (2.5% ± 2.9%); range 0%-9%

liver weights are not considered chemical related. At the 15-month interim evaluation, absolute and relative liver weights of exposed mice were similar to controls (Table F8). One male in the 15,000 ppm group and two females in the 5,000 ppm group had hepatocellular adenomas at the 15-month interim evaluation (Tables C1 and D1). At the end of the 2-year study, hepatocellular adenomas occurred with a statistically significant negative trend in males (30/50, 29/49, 19/51, 20/50) that was also significant by pairwise comparison in the 5,000 and 15,000 ppm groups (Table C3). Hepatocellular foci did not occur in an exposure-related pattern (foci of any type, males: 4/50, 16/49, 9/51, 1/50). The incidences of adenoma or foci in exposed females were similar to those of the controls (Tables D3 and D5).

GENETIC TOXICOLOGY

Manganese (II) sulfate monohydrate (100 to 10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 in tests at two laboratories (Table E1). All tests were performed with a preincubation protocol, with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9.

In cytogenetic tests with cultured Chinese hamster ovary cells, manganese (II) sulfate monohydrate induced sister chromatid exchanges with and without S9 activation (Table E2). Two of the three positive responses obtained in the absence of S9 required delayed cell culture harvest to offset severe manganese (II) sulfate monohydrate induced cytotoxicity; with S9, all positive responses were achieved with normal harvest times. Manganese (II) sulfate monohydrate also induced chromosomal aberrations in cultured Chinese hamster ovary cells in the absence of S9 (Table E3); as with the sister chromatid exchange test, the harvest time was extended to allow sufficient cells to accumulate for analysis. Increases in the percentage of cells with aberrations were not well correlated with the dose of manganese (II) sulfate monohydrate and occurred within a rather limited range (176 to 300 µg/mL). In the presence of S9, no significant increase in chromosomal aberrations was observed.

Manganese (II) sulfate monohydrate did not induce sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* treated with 12,500 ppm by feeding or 1,000 ppm administered by injection (Table E4).

TABLE 14
Incidences of Selected Lesions of the Forestomach of Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Dose (ppm)	0	1,500	5,000	15,000
Males				
2-Year Study				
Forestomach[a]	50	49	51	50
Erosion, Focal[b]	0	0	0	2 (3.0)[c]
Squamous Hyperplasia, Focal	2 (2.0)	1 (2.0)	5 (1.2)	14** (2.3)
Inflammation, Chronic Active	0	0	0	5* (2.0)
Ulcer	0	0	0	6* (2.5)
Squamous Cell Papilloma	1	1	0	0
Females				
9-Month Interim Evaluation				
Forestomach	10	0	0	9
Squamous Hyperplasia, Focal	0	0	0	1 (2.0)
15-Month Interim Evaluation				
Forestomach	9	0	1	9
Squamous Hyperplasia, Focal	0	0	1 (2.0)	1 (2.0)
Inflammation, Chronic Active	0	0	0	1 (1.0)
2-Year Study				
Forestomach	51	50	49	50
Squamous Hyperplasia, Focal	1 (2.0)	3 (1.7)	3 (2.0)	9** (2.4)
Ulcer	2 (2.0)	0	0	3 (2.7)
Inflammation, Chronic Active	0	1 (2.0)	1 (2.0)	3 (1.7)
Squamous Cell Papilloma	1	0	0	0

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

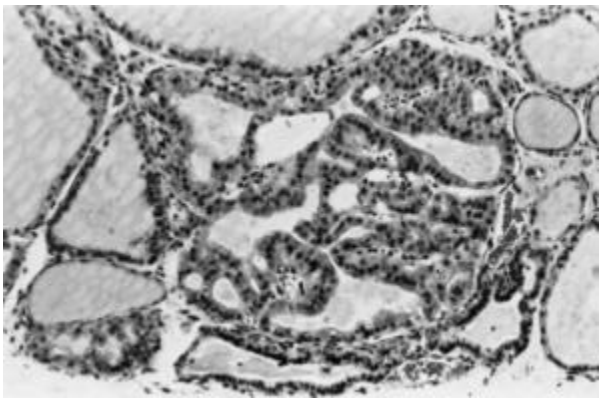

PLATE 1
Thyroid follicular cell hyperplasia in a female B6C3F$_1$ mouse exposed to15,000 ppm manganese sulfate in feed for 2 years. Note the papillary infolding of the follicular epithelium that partially obliterates the lumen of this enlarged follicle. H&E, 50X

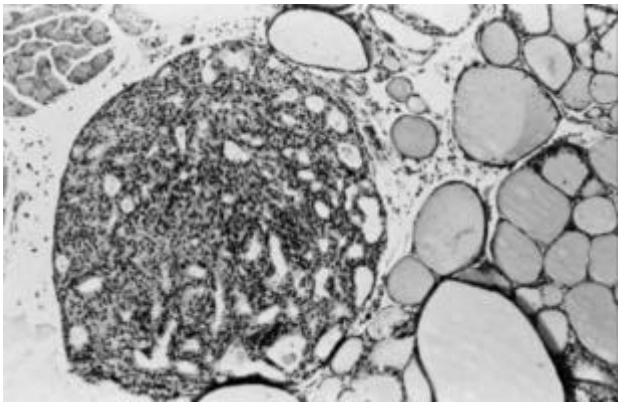

PLATE 2
Thyroid follicular cell adenoma in a male B6C3F$_1$ mouse exposed to 15,000 ppm manganese sulfate in feed for 2 years. Note the discrete, circumscribed mass adjacent to the dilated but otherwise normal thyroid follicles. H&E, 25X

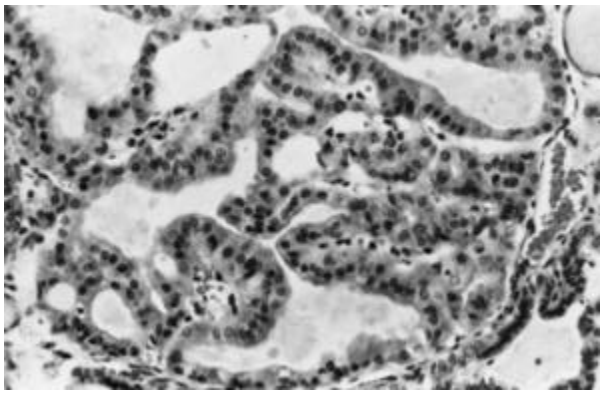

PLATE 3
Higher magnification of the follicular cell hyperplasia shown in Plate 1. The hyperplastic follicular epithelium consists of a single layer of cuboidal to columnar cells that are well differentiated. The papillary infoldings have a scant vascular stroma. H&E, 80X

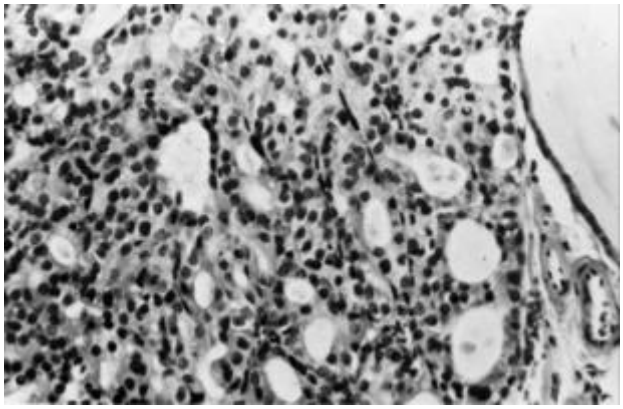

PLATE 4
Higher magnification of the follicular cell adenoma shown in Plate 3. The neoplastic follicular epithelium is cuboidal or low columnar, well differentiated, and arranged in small follicles or narrow cords without visible lumens. H&E, 80X

DISCUSSION AND CONCLUSIONS

Manganese does not occur naturally in elemental form but is a component of more than 100 minerals and is used primarily in the manufacture of steel. Manganese was nominated by the National Cancer Institute for toxicology and carcinogenesis studies because of its reported carcinogenicity in mice and widespread human exposure through food, drinking water, inhalation, and industrial emissions. The sulfate compound was chosen because of its stability, solubility, availability, and use as a dietary supplement for humans and animals.

The most consistent chemical-related changes associated with the ingestion of diets containing high levels of manganese (II) sulfate monohydrate in the 14-day and 13-week studies were lower body weight gains and absolute and relative liver weights. Although lower absolute liver weight usually accompanies and can be simply related to lower body weight gain, the relative liver weight is often unchanged or is slightly higher in these instances. However, in the studies of manganese (II) sulfate monohydrate, the relative and absolute liver weights were lower, indicating a direct effect of manganese on the hepatocytes. Hepatocytes are the predominant cellular component of the liver, and the lower absolute and relative liver weights probably reflect a reduction in the size and/or number of hepatocytes as well as a reduction in metabolic capacity.

Few studies have examined the mechanisms of manganese-induced injury to any tissue except the nervous system. Manganese preferentially accumulates in tissues and organs rich in mitochondria. The highest concentrations have been found in the endocrine glands, liver, kidney, and the pancreatic islets in particular (Venugopal and Luckey, 1978).

The mitochondrion is the major site of oxidative phosphorylation and ATP production needed for normal cellular metabolic activities. Excessive mitochondrial accumulation of manganese may have an adverse effect on the energy-generating pathways. The toxicity may also be related to the affinity for sulfhydryl groups to which manganese binds avidly, as do most heavy metals (Passow *et al.*, 1961). Sulfhydryl groups are components of many key enzymes and coenzymes in the energy-producing pathways. Binding with manganese might inhibit or reduce the activities of these enzymes, resulting in ATP depletion and, consequently, secondary cell injury.

The 14-day studies in rats and mice and the 13-week study in mice were conducted using doses as high as 50,000 ppm in feed; 25,000 ppm was the highest dose used in the 13-week study of rats. Several species differences were noted in the 14-day and 13-week studies. In the 14-day studies, the final mean body weight of male rats receiving 50,000 ppm was 13% lower than that of the controls, and both males and females receiving 50,000 ppm exhibited diarrhea. Similar effects were not observed in mice. In the 14-day studies, concentrations of manganese in the livers of rats receiving 50,000 ppm were approximately twice those of the controls; while in mice, manganese concentrations at this exposure level were 8 to 14 times higher than those in controls. In the 13-week study, all exposed male and 25,000 ppm female rats had lower absolute and relative liver weights than the controls; this effect was present but was less pronounced in exposed male mice. No effect on liver weights was observed in exposed female mice.

Effects of manganese exposure reported in the literature, which did not occur in these NTP studies, include degenerative changes in the seminiferous tubules (Shukla and Chandra, 1977) and in the adrenal cortex (Chandra and Imam, 1975). Some investigators have reported increases in percent hematocrit and mean cell volume (Baxter *et al.*, 1965) and depressed hemoglobin formation (Hartman *et al.*, 1955) following manganese exposure. These studies, however, used different species of animals, different routes of administration, different dosages, or different manganese compounds than the present NTP studies. Some minor changes were found in hematology parameters in the NTP studies, but these changes were not clearly related to the ingestion of manganese and are not consistent with the aforementioned studies. Khakimova *et al.* (1969) exposed male rats to 0.2 to 2.3 mg manganese sulfate in feed for 1 year and reported depressed thyroid gland activity, reduced thyroid weight, thinning of the follicular epithelium, and increased follicle diameter. In the present 2-year studies, the incidences of focal hyperplasia and follicular dilatation in the thyroid gland were significantly increased in

exposed male and female mice, with a slight increase in the incidence of adenoma. Thyroid gland effects, however, were not evident in rats. No mention of forestomach toxicity due to manganese exposure was found in the literature, but in the present 13-week studies of manganese (II) sulfate monohydrate, hyperkeratosis and hyperplasia occurred in 3 of 10 male mice given diets containing 50,000 ppm. In the 2-year studies, inflammation and ulcers of the forestomach were present only in male mice receiving 15,000 ppm, and the incidence of each lesion was significantly greater than that of the control. Significantly increased incidences of forestomach hyperplasia also occurred in male and female mice receiving 15,000 ppm in the 2-year feed studies. Although chronic manganese toxicity in humans produces central nervous system symptoms resembling parkinsonism (Rodier, 1955), these effects are not found in small laboratory animals (USEPA, 1984a) and did not occur in the NTP studies.

The doses selected for the 2-year NTP studies in rats and mice were 1,500, 5,000, and 15,000 ppm manganese (II) sulfate monohydrate in feed. In rats, this decision was based on the occurrence of diarrhea and lower body weight gain in 50,000 ppm males and females in the 14-day study, significantly lower absolute and relative liver weights in all male exposure groups (1,600 to 25,000 ppm) and in the 25,000 ppm female group in the 13-week study, and marginally lower body weight gains in the male 12,500 and 25,000 ppm groups and significantly lower body weight gains in 6,250, 12,500, and 25,000 ppm females in the 13-week study. Dose selection for mice was based on significantly lower body weight gains in exposed males and in 50,000 ppm females and on significantly lower absolute and relative liver weights in 50,000 ppm males in the 13-week studies. Doses of manganese many times higher than the recommended dietary allowance for good nutrition in rodents might also produce complicating disturbances in the metabolism of other essential trace elements such as iron, copper, and zinc. The National Research Council had stated that the recommended dietary allowance of manganese for rats is 50 mg/kg of diet and for mice is 45 mg/kg of diet. Thus, the high dose of 15,000 ppm manganese (II) sulfate monohydrate chosen for the 2-year studies in rats and mice is equivalent to 4,800 mg of manganese per kg of feed or 96 times the recommended dietary allowance for rats and 107 times that for mice. Control animals receiving the NIH-07 diet were exposed to approximately 92 ppm manganese (approximately 2 ounces per ton).

The findings in these 2-year feed studies do not provide evidence of a deleterious effect of manganese (II) sulfate monohydrate on the metabolism of other essential trace metals. Gubler *et al.* (1954) investigated the influence of manganese on the metabolism of copper in male rats, finding that the ingestion of large amounts of manganese chloride (4%) in feed over a period of 120 days was associated with an increase in the concentration of copper in plasma and brain, a decrease in the concentration of copper in the kidney, and no effect on copper levels in the liver; additionally, the concentration of iron in the liver was significantly reduced. The NTP manganese (II) sulfate monohydrate study data for male rats at the 9- and 15-month interim evaluations do not show similar copper concentration patterns, but concentrations of iron in the livers of exposed animals were lower than controls, often significantly, in male and female rats and mice. Despite the lower iron levels, no indications of anemia or iron deficiency occurred. Other studies (Hartman *et al.*, 1955) have shown that the addition of manganese to the diet of lambs depleted of iron resulted in depressed hemoglobin concentrations, indicating that manganese was interfering with iron absorption rather than hematopoiesis. The interaction of iron and manganese metabolism was also studied by Diez-Ewald *et al.* (1968) in rats. Manganese absorption increased with increased iron absorption in iron-deficient animals; in animals not iron deficient, iron absorption decreased with decreased manganese absorption. However in iron-deficient animals, the increase in manganese absorption was accompanied by a compensatory increase in manganese excretion, and in animals not iron deficient, the decrease in manganese absorption accompanied a decrease in manganese excretion.

The mean body weight of 15,000 ppm male rats was consistently lower than that of the control group throughout the 2-year study, and the final mean body weight was 10% lower. Survival of 15,000 ppm male rats in the 2-year study was also significantly lower than that of the control group. Despite the reduced final survival of 15,000 ppm males, the study was considered adequate for assessing the carcinogenic potential of manganese (II) sulfate monohydrate, since a sufficient number of rats lived long enough to be at risk for development of neoplasia. After 93 weeks, the survival rate for 15,000 ppm and control male rats was 67%. The reduced survival of 15,000 ppm males resulted from the increased incidences of marked nephropathy and renal failure in this group. The increased severity of

nephropathy in the 15,000 ppm male rats was attributed to the ingestion of manganese (II) sulfate monohydrate.

Survival of mice in the 2-year feed study was similar to that of controls. The mean body weights of 15,000 ppm male mice were slightly lower than, but within 5% of, that of the control group throughout the study. Although slight, this decrease may be chemical related. In female mice, the decreases in mean body weights were exposure related; the final mean body weights of the 1,500, 5,000, and 15,000 ppm groups were 6%, 9%, and 13% lower than that of the control group. Toxicity also occurred in the thyroid and forestomach of male and female mice. Incidences of thyroid follicular dilatation and focal hyperplasia in the 15,000 ppm males and females were increased significantly. In the forestomach, the incidence of focal hyperplasia was also increased significantly in the 15,000 ppm males and females and was accompanied by increased incidences of ulceration/erosion and inflammation. Because of these findings, the doses used in the 2-year mouse study were considered adequate for the determination of the potential carcinogenicity of manganese (II) sulfate monohydrate.

In these 2-year feed studies, manganese (II) sulfate monohydrate did not cause a significant increase in the incidence of neoplasia in rats or mice. In rats, the only indication of a possible carcinogenic effect occurred in the pancreatic islets where the incidences of hyperplasia and adenoma were slightly higher in exposed males than in the control group. While an effect on the endocrine pancreas is plausible in view of the preferential accumulation of manganese in this organ, the occurrence of neither hyperplasia nor adenoma was exposure related or statistically significant. Furthermore, the adenoma rates of 8% in the 5,000 ppm group and 6% in the 15,000 ppm group are well within the range of 0% to 12% in the historical controls. Therefore, the incidence of adenoma in the pancreatic islets in male rats is not considered a carcinogenic effect of manganese (II) sulfate monohydrate.

Other than the forestomach effects, the principal lesions in mice associated with the ingestion of manganese (II) sulfate monohydrate were found in the thyroid gland. Significantly increased incidences of follicular dilatation and focal hyperplasia of the follicular epithelium were found in 15,000 ppm males and exposed females. The occurrence of follicular dilatation in mice is consistent with the report of Khakimova *et al.* (1969) of depressed thyroid gland activity, reduced thyroid gland weight, thinning of the follicular epithelium, and increased follicular diameter in rats given manganese sulfate in feed for 1 year. While the mechanism of this effect is unknown, manganese (II) is believed to regulate the activities of a number of cellular enzymes, including pyruvate carboxylase, P-enolpyruvate carboxykinase, fructose1,6-bisphosphatase, insulin receptor protein kinase, phosphorylase kinase, arginase, and superoxide dismutase (Schramm, 1986). Thus, it is plausible that high dietary levels of manganese resulted in depressed thyroid gland activity and less than optimal production of triiodothyronine and thyroxine. Reduced thyroid activity due to the ingestion of manganese might produce a compensatory increase in the synthesis and release of thyroid stimulating hormone from the pituitary gland as is observed with goitrogenic chemicals (Hill *et al.*, 1989). The prolonged stimulation of the thyroid gland by thyroid stimulating hormone is known to cause hyperplasia and neoplasia.

In male mice, follicular cell adenomas occurred only in the 15,000 ppm group and at a rate of 6%, as compared to the average rate of 2% and range of 0% to 4% for historical control groups. Furthermore, the incidence of follicular cell adenomas of 10% in 15,000 ppm females was also slightly above the range of 0% to 9% for historical controls. While the incidences of follicular cell adenomas in exposed mice were not significantly greater than those of the controls, the slight increase in incidence relative to the historical control range and supported by the increased incidence of follicular cell hyperplasia was considered to provide equivocal evidence of carcinogenic activity.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of manganese (II) sulfate monohydrate in male or female F344/N rats receiving 1,500, 5,000, or 15,000 ppm. There was *equivocal evidence of carcinogenic activity* of manganese (II) sulfate monohydrate in male and female $B6C3F_1$ mice, based on the marginally increased incidences of thyroid gland follicular cell adenoma and the significantly increased incidences of follicular cell hyperplasia.

The ingestion of diets containing manganese (II) sulfate monohydrate was associated with an increased severity of nephropathy in male rats, focal squamous hyperplasia of the forestomach in male and female mice, and ulcers and inflammation of the forestomach in male mice. These studies were not designed to assess any neurotoxicity that might have been expected with chronic exposure to sufficiently high doses of manganese.

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

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF MANGANESE (II) SULFATE MONOHYDRATE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	8	10	10	10
15-Month interim evaluation[c]	10	9	9	8
Early deaths				
Moribund	21	24	24	38
Natural deaths	6	10	5	7
Survivors				
Died last week of study			1	
Terminal sacrifice	25	17	21	7
Animals examined microscopically	70	70	70	70
15-Month Interim Evaluation				
Endocrine System				
Thyroid gland	(10)			(8)
C-cell, carcinoma				1 (13%)
Genital System				
Preputial gland	(10)	(1)	(1)	(8)
Adenoma		1 (100%)	1 (100%)	
Testes	(10)	(2)		(8)
Bilateral, interstitial cell, adenoma	1 (10%)	1 (50%)		
Interstitial cell, adenoma	1 (10%)	1 (50%)		2 (25%)
Nervous System				
Brain	(10)			(8)
Granular cell tumor benign	1 (10%)			
Respiratory System				
Lung	(10)			(8)
Alveolar/bronchiolar adenoma	1 (10%)			
Special Senses System				
Zymbal's gland	(1)			
Carcinoma	1 (100%)			
2-Year Study				
Alimentary System				
Intestine large, cecum	(52)	(50)	(50)	(51)
Intestine large, colon	(52)	(51)	(50)	(52)
Intestine large, rectum	(52)	(51)	(51)	(52)
Histiocytic sarcoma	1 (2%)			
Polyp adenomatous				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Intestine small, duodenum	(52)	(51)	(51)	(52)
Intestine small, ileum	(52)	(50)	(51)	(51)
Intestine small, jejunum	(52)	(51)	(51)	(51)
Polyp adenomatous			1 (2%)	
Liver	(52)	(51)	(51)	(52)
Hepatocellular adenoma			1 (2%)	
Hepatocellular adenoma, multiple		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Mesentery	(6)	(9)	(5)	(6)
Pancreas	(52)	(50)	(51)	(51)
Acinus, adenoma		2 (4%)	1 (2%)	
Pharynx	(1)			
Papilloma squamous	1 (100%)			
Salivary glands	(52)	(47)	(51)	(51)
Stomach, forestomach	(52)	(51)	(51)	(52)
Papilloma squamous			1 (2%)	
Papilloma squamous, multiple				1 (2%)
Stomach, glandular	(52)	(51)	(51)	(52)
Tongue	(1)			
Papilloma squamous	1 (100%)			
Tooth	(51)	(50)	(51)	(51)
Gingiva, squamous cell carcinoma			1 (2%)	
Cardiovascular System				
Heart	(52)	(51)	(51)	(52)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Endocrine System				
Adrenal gland, cortex	(52)	(51)	(51)	(52)
Adenoma	1 (2%)			1 (2%)
Adrenal gland, medulla	(52)	(51)	(51)	(52)
Pheochromocytoma malignant	1 (2%)		1 (2%)	
Pheochromocytoma complex		1 (2%)	1 (2%)	
Pheochromocytoma benign	9 (17%)	12 (24%)	12 (24%)	4 (8%)
Bilateral, pheochromocytoma benign	5 (10%)	5 (10%)	2 (4%)	2 (4%)
Islets, pancreatic	(52)	(50)	(51)	(51)
Adenoma		3 (6%)	4 (8%)	3 (6%)
Carcinoma				1 (2%)
Mixed tumor benign		1 (2%)		
Parathyroid gland	(51)	(46)	(49)	(50)
Adenoma	1 (2%)			
Pituitary gland	(52)	(49)	(51)	(50)
Ependymoma malignant, metastatic, brain				1 (2%)
Pars distalis, adenoma	13 (25%)	12 (24%)	14 (27%)	14 (28%)
Pars distalis, adenoma, multiple			1 (2%)	1 (2%)
Pars distalis, carcinoma			1 (2%)	
Pars intermedia, adenoma			1 (2%)	
Pars intermedia, carcinoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(52)	(48)	(51)	(51)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	6 (12%)	6 (13%)	7 (14%)	4 (8%)
C-cell, adenoma, multiple		1 (2%)		
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Follicular cell, carcinoma		2 (4%)		
General Body System				
None				
Genital System				
Epididymis	(52)	(51)	(51)	(52)
Preputial gland	(52)	(51)	(51)	(52)
Adenoma	3 (6%)	1 (2%)	1 (2%)	
Carcinoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Bilateral, carcinoma			3 (6%)	
Prostate	(52)	(51)	(51)	(52)
Seminal vesicle	(52)	(51)	(51)	(52)
Testes	(52)	(51)	(51)	(52)
Bilateral, interstitial cell, adenoma	35 (67%)	30 (59%)	33 (65%)	31 (60%)
Interstitial cell, adenoma	11 (21%)	12 (24%)	9 (18%)	10 (19%)
Hematopoietic System				
Blood	(46)	(42)	(44)	(41)
Bone marrow	(52)	(51)	(51)	(52)
Femoral, fibrosarcoma	1 (2%)			
Lymph node	(52)	(51)	(51)	(52)
Renal, carcinoma, metastatic, kidney				1 (2%)
Lymph node, mandibular	(51)	(47)	(51)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Lymph node, mesenteric	(51)	(50)	(51)	(51)
Spleen	(52)	(51)	(51)	(52)
Fibrosarcoma			1 (2%)	
Hemangioma	1 (2%)			
Thymus	(49)	(47)	(49)	(45)
Integumentary System				
Mammary gland	(45)	(38)	(36)	(39)
Fibroadenoma	1 (2%)		1 (3%)	2 (5%)
Skin	(49)	(51)	(50)	(52)
Basal cell adenoma			2 (4%)	
Basal cell carcinoma	1 (2%)		1 (2%)	
Basosquamous tumor benign			1 (2%)	
Keratoacanthoma	1 (2%)		1 (2%)	
Keratoacanthoma, multiple				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Integumentary System (continued)				
Skin (continued)	(49)	(51)	(50)	(52)
Papilloma squamous			1 (2%)	1 (2%)
Squamous cell carcinoma	1 (2%)	1 (2%)		
Trichoepithelioma			1 (2%)	
Subcutaneous tissue, fibroma				1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, fibrous histiocytoma				2 (4%)
Subcutaneous tissue, lipoma			1 (2%)	
Subcutaneous tissue, neurofibroma			1 (2%)	
Subcutaneous tissue, neurofibrosarcoma	2 (4%)	1 (2%)		
Musculoskeletal System				
Bone	(52)	(51)	(51)	(52)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Squamous cell carcinoma, metastatic, tooth			1 (2%)	
Femur, fibrosarcoma	1 (2%)			
Skeletal muscle	(52)	(51)	(51)	(52)
Nervous System				
Brain	(52)	(50)	(51)	(52)
Astrocytoma malignant	2 (4%)			
Carcinoma, metastatic, pituitary gland		1 (2%)	1 (2%)	
Ependymoma malignant				1 (2%)
Spinal cord	(1)	(2)		(1)
Glioma benign	1 (100%)			
Respiratory System				
Lung	(52)	(51)	(51)	(52)
Alveolar/bronchiolar adenoma		3 (6%)		
Alveolar/bronchiolar carcinoma	2 (4%)			1 (2%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma	1 (2%)			
Neurofibrosarcoma, metastatic, uncertain primary site	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal gland	1 (2%)			
Nose	(52)	(50)	(51)	(52)
Papilloma squamous		1 (2%)		
Special Senses System				
Ear		(1)		(1)
Fibrosarcoma				1 (100%)
Papilloma squamous, multiple		1 (100%)		
Zymbal's gland	(1)	(1)	(1)	
Adenoma			1 (100%)	
Carcinoma	1 (100%)	1 (100%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(52)	(50)	(51)	(52)
Lipoma		1 (2%)		
Renal tubule, adenoma	1 (2%)	2 (4%)		1 (2%)
Renal tubule, oncocytoma benign		1 (2%)	1 (2%)	
Urinary bladder	(52)	(50)	(51)	(52)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[d]	(52)	(51)	(51)	(52)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	32 (62%)	31 (61%)	30 (59%)	25 (48%)
Mesothelioma malignant	2 (4%)	2 (4%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[e]				
15-Month interim evaluation	4	3	1	3
2-Year study	50	47	49	51
Total primary neoplasms				
15-Month interim evaluation	5	3	1	3
2-Year study	143	140	140	115
Total animals with benign neoplasms				
15-Month interim evaluation	4	3	1	2
2-Year study	49	45	48	47
Total benign neoplasms				
15-month interim evaluation	4	3	1	2
2-Year study	93	97	100	81
Total animals with malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	37	38	34	30
Total malignant neoplasms				
15-Month interim evaluation	1			1
2-Year study	50	43	40	34
Total animals with metastatic neoplasms				
2-Year study	2	2	2	4
Total metastatic neoplasms				
2-Year study	2	2	2	5
Total animals with malignant neoplasms uncertain primary site				
2-Year study	1			

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were observed at any site in any animal at the 9-month interim evaluation.
[c] No neoplasms were observed in the alimentary, cardiovascular, general body, hematopoietic, integumentary, musculoskeletal, and urinary systems in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm

Number of Days on Study	0 9 5	2 6 9	4 5 6	4 9 5	5 2 6	5 4 7	5 6 2	5 7 1	5 7 8	5 9 0	6 0 3	6 0 3	6 1 0	6 1 2	6 2 1	6 2 7	6 4 2	6 5 5	6 7 0	6 7 3	6 7 3	6 7 7	6 9 0	6 9 1	6 9 5	7 0 1	7 2 6
Carcass ID Number	0 1 0 4	0 0 9 4	0 1 2 2	1 1 4 3	0 0 1 2	0 0 9 5	1 0 2 2	0 1 1 5	1 1 3 3	1 0 3 3	0 5 1 3	1 1 3 3	1 2 3 3	0 8 4 3	1 0 1 3	0 5 2 3	1 1 4 3	0 4 1 3	0 2 3 3	0 9 3 3	1 1 5 3	1 2 4 3	0 5 3 3	0 3 5 3	1 2 5 3	0 4 5 3	0 2 5 3
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																											
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																											
Mesentery			+														+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																											
Papilloma squamous																											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																											
Papilloma squamous																											
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																											X
Pheochromocytoma benign															X	X										X	X
Bilateral, pheochromocytoma benign																						X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																											
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X									X	X		X	X		X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X					X																		
Follicular cell, adenoma																					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 Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	732	732	732	732	732	
Carcass ID Number	00442	00444	00663	00774	00775	01112	01144	01013	01014	01022	02024	02032	03034	03061	06162	06264	06373	08181	09191	01051	01131	01332	01335	01441	01445	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																X										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																X										1
Mesentery	+			+					+													+				6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pharynx																		+								1
Papilloma squamous																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tongue											+															1
Papilloma squamous											X															1
Tooth	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma malignant																										1
Pheochromocytoma benign				X								X		X						X		X				9
Bilateral, pheochromocytoma benign			X		X			X															X			5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pars distalis, adenoma					X	X	X				X	X							X				X			13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell, adenoma		X		X														X		X						6
Follicular cell, adenoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	0 9 5	2 6 9	4 5 6	4 9 5	5 2 6	5 4 7	5 6 2	5 7 1	5 7 8	5 9 0	6 0 3	6 0 3	6 1 0	6 1 2	6 2 1	6 2 7	6 4 2	6 5 5	6 7 0	6 7 3	7 7 3	7 7 7	7 9 0	7 9 1	7 9 5	7 0 1	7 2 6
Carcass ID Number	0 1 0 4	0 0 9 4	0 1 2 2	1 1 4 3	0 0 1 2	0 0 9 5	0 1 0 2	0 1 1 5	0 1 3 3	0 1 0 3	0 1 1 3	0 1 2 3	0 1 2 8	0 1 0 1	0 1 0 5	0 1 1 2	0 1 1 4	0 1 4 1	0 2 2 3	0 9 3 3	1 1 1 5	1 2 2 4	0 5 5 3	0 3 3 5	1 2 2 5	0 4 4 5	0 2 2 5
General Body System																											
None																											
Genital System																											
Coagulating gland																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																											
Carcinoma								X								X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X				X	X		X			X		X			X		X	X	X	X	X	
Interstitial cell, adenoma			X					X			X		X	X					X		X						X
Hematopoietic System																											
Blood	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	M	+	M
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, fibrosarcoma																											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																											
Mammary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M
Fibroadenoma																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Basal cell carcinoma																											
Keratoacanthoma																							X				
Squamous cell carcinoma																									X		
Subcutaneous tissue, fibrosarcoma				X																							
Subcutaneous tissue, neurofibrosarcoma																				X							
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, fibrosarcoma																											
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant								X																			
Peripheral nerve																											
Spinal cord																											
Glioma benign																											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	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	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 0 4 2	0 0 4 4	0 0 6 3	0 0 7 4	0 0 7 5	0 1 1 2	0 1 4 4	0 1 1 3	0 0 1 4	0 0 2 2	0 0 2 4	0 0 3 2	0 0 3 4	0 0 6 1	0 0 6 2	0 0 6 4	0 0 7 3	0 0 8 1	0 0 9 1	0 1 0 5	0 1 3 1	0 1 3 2	0 1 3 3	0 1 3 5	0 1 4 1	0 1 4 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Coagulating gland																						+				1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma								X				X	X													3
Carcinoma																										2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, interstitial cell, adenoma	X	X	X	X		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	35
Interstitial cell, adenoma					X		X			X																11
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Femoral, fibrosarcoma															X											1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangioma																X										1
Thymus	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Fibroadenoma						X																				1
Skin	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Basal cell carcinoma																							X			1
Keratoacanthoma																										1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, neurofibrosarcoma								X																		2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Femur, fibrosarcoma															X											1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Astrocytoma malignant			X																							2
Peripheral nerve																						+				1
Spinal cord																						+				1
Glioma benign																						X				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	732	732	732	732	732	732	
Carcass ID Number	00042	00044	00063	00074	00075	00112	00144	00113	00141	00222	00224	00232	00340	00341	00622	00644	00733	00811	00911	01055	01131	01232	01335	01441	01445	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																			X				X			2
Histiocytic sarcoma																X										1
Neurofibrosarcoma, metastatic, uncertain primary site																										1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																										
Eye																										3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Renal tubule, adenoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional epithelium, papilloma																		X								1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Histiocytic sarcoma																X										1
Leukemia mononuclear	X	X	X	X		X		X	X		X		X	X	X			X	X	X		X	X		X	32
Mesothelioma malignant				X																						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm

Number of Days on Study	1 2 4	3 3 3	3 4 6	4 5 1	4 6 6	5 3 2	5 7 8	5 9 0	6 1 3	6 1 3	6 1 3	6 3 5	6 4 2	6 5 2	6 5 8	6 5 9	6 6 6	6 6 6	6 7 0	6 7 4	6 7 7	6 8 2	6 8 3	6 8 4	6 9 0	6 9 4
Carcass ID Number	0 2 5 4	0 2 4 2	0 2 8 1	0 1 8 4	0 1 7 1	0 2 8 2	0 1 7 5	0 2 5 3	0 1 6 1	0 1 9 5	0 2 7 1	0 1 8 1	0 1 9 3	0 1 7 3	0 2 4 1	0 2 2 5	0 2 0 2	0 2 2 4	0 1 8 2	0 1 6 3	0 2 1 3	0 2 4 4	0 2 6 5	0 2 4 5	0 2 2 2	0 1 8 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma, multiple																						X				
Mesentery																						+		+		
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																				X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																										
Pheochromocytoma benign									X							X			X					X		
Bilateral, pheochromocytoma benign												X										X				X
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																X	
Mixed tumor benign																				X						
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X								X	X	X				X			
Pars intermedia, carcinoma							X																			
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma															X											
C-cell, adenoma				X																				X		
C-cell, adenoma, multiple														X												
Follicular cell, adenoma																						X				
Follicular cell, carcinoma																								X		
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	6 9 4	6 9 8	7 1 1	7 1 7	7 2 3	7 2 6	7 2 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2 1	0 1 7 2	0 1 5 3	0 2 6 4	0 2 3 2	0 2 5 2	0 2 7 2	0 2 7 3	0 1 5 2	0 1 5 4	0 1 7 4	0 1 9 1	0 2 0 1	0 1 5 5	0 2 0 3	0 2 0 5	0 2 1 2	0 2 1 4	0 2 2 3	0 2 3 1	0 2 3 5	0 2 5 5	0 2 6 1	0 2 6 3	0 2 8 3	0 2 8 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma, multiple																										1
Mesentery	+	+				+		+								+	+	+								9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																X										2
Salivary glands	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma complex																			X							1
Pheochromocytoma benign			X	X		X	X	X			X							X					X			12
Bilateral, pheochromocytoma benign	X	X																								5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		3
Mixed tumor benign																										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X										X	X	X	X		X									X	12
Pars intermedia, carcinoma																										1
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, C-cell, adenoma																										1
C-cell, adenoma				X						X		X									X					6
C-cell, adenoma, multiple																										1
Follicular cell, adenoma																										1
Follicular cell, carcinoma				X																						2
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	1 2 4	3 3 3	3 4 6	4 5 1	4 6 6	5 3 2	5 7 8	5 9 0	6 1 3	6 1 3	6 1 3	6 3 5	6 4 2	6 5 2	6 5 8	6 5 9	6 6 6	6 6 6	6 7 0	6 7 4	6 7 7	6 8 2	6 8 3	6 8 4	6 9 0	6 9 4
Carcass ID Number	0 2 5 4	0 2 4 2	0 2 8 1	0 1 8 4	0 1 7 1	0 2 8 2	0 1 7 5	0 2 5 3	0 1 6 1	0 1 9 5	0 2 7 1	0 1 8 1	0 1 9 3	0 1 7 3	0 2 4 1	0 2 2 5	0 2 0 2	0 2 2 4	0 1 8 2	0 1 6 3	0 2 1 3	0 2 4 4	0 2 6 5	0 2 4 5	0 2 2 2	0 1 8 3
Genital System																										
Coagulating gland																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																						+				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma									X						X											
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			X
Hematopoietic System																										
Blood	+	+	+	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	M	+	+	+	M
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin		X																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	M	M	+	+	+	+	+	M	M	M	M	M	M	+	+	+	+	M	M	+	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																										
Subcutaneous tissue, fibrosarcoma		X																								
Subcutaneous tissue, neurofibrosarcoma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland							X																			
Peripheral nerve			+											+												
Spinal cord			+											+												
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	6 9 4	6 9 8	7 1 1	7 1 7	7 2 3	7 2 6	7 2 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2 1	0 1 7 2	0 1 5 3	0 2 6 4	0 2 3 2	0 2 5 2	0 2 7 2	0 2 7 3	0 1 5 2	0 1 5 4	0 1 7 4	0 1 9 1	0 2 0 1	0 1 5 5	0 2 0 3	0 2 0 5	0 2 1 2	0 2 1 4	0 2 2 3	0 2 3 1	0 2 5 5	0 2 6 1	0 2 6 3	0 2 8 3	0 2 8 4	Total Tissues/ Tumors
Genital System																									
Coagulating gland									+		+	+													3
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Penis																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma	X																								1
Carcinoma																									2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X			X	X	X	X	X			X	X	X		X	X	X	X	30
Interstitial cell, adenoma									X	X							X				X				12
Hematopoietic System																									
Blood	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma, metastatic, skin																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma											X														1
Subcutaneous tissue, fibrosarcoma																									1
Subcutaneous tissue, neurofibrosarcoma			X																						1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																									
Brain	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																									1
Peripheral nerve																									2
Spinal cord																									2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma			X																					X	3
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																	X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	1 2 4	3 3 3	3 4 6	4 5 1	4 6 6	5 3 2	5 7 8	5 9 0	6 1 3	6 1 3	6 1 3	6 3 5	6 4 2	6 5 2	6 5 8	6 5 9	6 6 6	6 6 6	6 7 0	6 7 4	6 7 7	6 8 2	6 8 3	6 8 4	6 9 0	6 9 4
Carcass ID Number	0 2 5 4	0 2 4 2	0 2 8 1	0 1 8 4	0 1 7 1	0 2 8 2	0 1 7 5	0 2 5 3	0 1 6 1	0 1 9 5	0 2 7 1	0 1 8 1	0 1 9 3	0 1 7 3	0 2 4 1	0 2 2 5	0 2 0 2	0 2 2 4	0 1 8 2	0 1 6 3	0 2 1 3	0 2 4 4	0 2 6 5	0 2 4 5	0 2 2 2	0 1 8 3
Special Senses System																										
Ear																										
Papilloma squamous, multiple																										
Eye														+												
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland				+																						
Carcinoma				X																						
Urinary System																										
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																										
Renal tubule, adenoma																										
Renal tubule, oncocytoma benign														X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X					X	X	X			X				X	X	X		X	X	X
Mesothelioma malignant																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	6 9 4	6 9 8	7 1 1	7 1 7	7 2 3	7 2 6	7 2 6	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2 1	0 1 7 2	0 1 5 3	0 2 6 4	0 2 3 2	0 2 5 2	0 2 7 2	0 2 7 3	0 1 5 2	0 1 5 4	0 1 7 4	0 1 9 1	0 2 0 1	0 1 5 5	0 2 0 3	0 2 0 5	0 2 1 2	0 2 1 4	0 2 2 3	0 2 3 1	0 2 5 5	0 2 6 1	0 2 6 3	0 2 8 3	0 2 8 4	Total Tissues/ Tumors
Special Senses System																									
Ear					+																				1
Papilloma squamous, multiple					X																				1
Eye																+									2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Zymbal's gland																									1
Carcinoma																									1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																X									1
Renal tubule, adenoma		X																					X		2
Renal tubule, oncocytoma benign																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear		X	X	X	X		X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	31
Mesothelioma malignant				X		X																			2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm

Number of Days on Study	3 8 0	4 1 7	4 8 1	4 9 9	5 0 9	5 1 9	5 2 8	5 2 8	5 5 7	5 8 2	6 0 6	6 1 3	6 1 8	6 2 1	6 3 1	6 3 5	6 5 4	6 5 9	6 6 3	6 8 4	6 9 0	6 9 8	7 0 1	7 0 3	7 1 1	7 1 4
Carcass ID Number	0 3 3 4	0 3 5 4	0 3 6 4	0 3 7 4	0 3 9 2	0 3 8 5	0 2 9 1	0 2 9 3	0 3 7 1	0 4 0 2	0 3 1 1	0 4 2 4	0 3 0 4	0 4 0 5	0 3 1 2	0 3 3 3	0 3 2 5	0 3 3 2	0 2 9 4	0 3 6 5	0 3 1 4	0 3 9 3	0 3 5 2	0 3 3 1	0 3 2 4	0 3 2 2
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																										
Mesentery																		+							+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																								X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																						X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gingiva, squamous cell carcinoma																										
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma complex																										
Pheochromocytoma benign													X				X	X	X					X		
Bilateral, pheochromocytoma benign																							X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X	X		
Parathyroid gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X	X								X	X					X		X			X	
Pars distalis, adenoma, multiple													X													
Pars distalis, carcinoma									X																	
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X						X		X							X					
Follicular cell, adenoma														X												
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 1 5	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 1 5	0 3 4 2	0 3 0 5	0 3 0 1	0 3 4 4	0 3 5 3	0 3 9 1	0 3 1 3	0 3 1 5	0 3 2 3	0 3 3 5	0 3 5 1	0 3 7 2	0 3 5 5	0 3 8 1	0 3 8 2	0 3 8 3	0 3 8 4	0 3 9 5	0 3 0 3	0 4 1 1	0 4 1 3	0 4 1 4	0 4 2 1	0 4 2 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp adenomatous									X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma																X										1
Mesentery										+	+						+									5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gingiva, squamous cell carcinoma				X																						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma malignant																X										1
Pheochromocytoma complex												X														1
Pheochromocytoma benign	X					X			X		X				X				X		X					12
Bilateral, pheochromocytoma benign																		X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X															X					4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma					X		X	X	X						X	X										14
Pars distalis, adenoma, multiple																										1
Pars distalis, carcinoma																										1
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma							X		X			X														7
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	3 8 0	4 1 7	4 8 1	4 9 9	5 0 9	5 1 9	5 2 8	5 2 8	5 5 7	5 8 2	6 0 6	6 1 3	6 1 8	6 2 1	6 3 1	6 3 5	6 5 4	6 5 9	6 6 3	6 8 4	6 9 0	6 9 8	7 0 1	7 0 3	7 1 1	7 1 4
Carcass ID Number	0 3 3 4	0 3 5 4	0 3 6 4	0 3 7 4	0 3 9 2	0 3 8 5	0 2 9 1	0 2 9 3	0 3 7 1	0 4 0 2	0 3 1 1	0 4 2 4	0 3 0 4	0 4 0 5	0 3 1 2	0 3 3 3	0 3 2 5	0 3 3 2	0 2 9 4	0 3 6 5	0 3 1 4	0 3 9 3	0 3 5 2	0 3 3 1	0 3 2 4	0 3 2 2
Genital System																										
Coagulating gland																				+						
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma																		X								
Bilateral, carcinoma																								X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X					X		X		X				X		X	X	X	X	X	X			X
Interstitial cell, adenoma							X				X						X			X					X	
Hematopoietic System																										
Blood	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																										
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	M	+	M	+	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+
Fibroadenoma																				X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																				X						
Basal cell carcinoma																										X
Basosquamous tumor benign																										
Keratoacanthoma																										X
Papilloma squamous																X										
Trichoepithelioma																										X
Subcutaneous tissue, lipoma																										X
Subcutaneous tissue, neurofibroma													X													
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, tooth																										
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland									X																	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 1 5	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 1 5	0 3 4 2	0 3 0 5	0 3 0 1	0 3 4 4	0 3 5 3	0 3 9 1	0 3 1 3	0 3 1 5	0 3 2 3	0 3 3 5	0 3 5 1	0 3 7 2	0 3 5 5	0 3 8 1	0 3 8 2	0 3 8 3	0 3 8 4	0 3 9 5	0 4 0 3	0 4 1 1	0 4 1 3	0 4 1 4	0 4 2 1	0 4 2 5	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																		X								1
Carcinoma																										1
Bilateral, carcinoma											X														X	3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X		X	X	X	33
Interstitial cell, adenoma									X	X		X										X				9
Hematopoietic System																										
Blood	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma												X														1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	M	+	M	+	M	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	36
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma							X																			2
Basal cell carcinoma																										1
Basosquamous tumor benign																				X						1
Keratoacanthoma																										1
Papilloma squamous																										1
Trichoepithelioma																										1
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, neurofibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell carcinoma, metastatic, tooth				X																						1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 1 5	7 2 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 4 1 5	0 3 4 2	0 3 0 5	0 3 0 1	0 3 4 4	0 3 5 3	0 3 9 1	0 3 1 3	0 3 1 5	0 3 2 3	0 3 3 5	0 3 5 1	0 3 7 2	0 3 5 5	0 3 8 1	0 3 8 2	0 3 8 3	0 3 8 4	0 3 9 5	0 3 0 3	0 4 1 1	0 4 1 3	0 4 1 4	0 4 2 1	0 4 2 5	Total Tissues/ Tumors
Special Senses System																										
Eye		+	+												+											6
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Zymbal's gland										+																1
Adenoma										X																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Renal tubule, oncocytoma benign													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear	X						X		X		X	X		X	X	X	X	X		X	X	X	X	X		30

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm

Number of Days on Study	268	275	354	498	498	527	557	568	618	626	631	631	632	632	638	638	652	655	660	600	661	611	663	670	673	677
Carcass ID Number	05044	04644	05244	44043	44491	45453	52525	49545	44044	47343	49924	56334	44545	53345	54545	46363	51365	56434	43342	44242	51252	56161	48485	48282	43535	49494
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous								X																		
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+												+		+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous, multiple																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									X	
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X		
Bilateral, pheochromocytoma benign																						X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenoma												X														
Carcinoma																							X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Ependymoma malignant, metastatic, brain													X													
Pars distalis, adenoma									X			X								X	X			X		
Pars distalis, adenoma, multiple																							X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X					X							X			
Follicular cell, adenoma						X																				
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 7	6 8 7	6 9 0	6 9 1	6 9 8	7 0 1	7 0 7	7 1 1	7 1 3	7 1 3	7 1 5	7 1 5	7 1 5	7 1 9	7 2 6	7 2 6	7 2 7	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	0 4 5 4	0 4 7 5	0 5 4 2	0 4 8 4	0 4 3 1	0 5 2 3	0 5 4 3	0 5 3 5	0 5 0 3	0 5 1 1	0 5 6 2	0 5 3 1	0 5 5 1	0 5 5 2	0 5 0 2	0 4 5 1	0 5 2 1	0 5 4 1	0 5 3 2	0 4 3 2	0 4 4 1	0 4 6 1	0 5 1 5	0 5 5 3	0 5 5 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Polyp adenomatous																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Mesentery					+					+									+							6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Papilloma squamous, multiple																X										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	51
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma benign							X						X	X												4
Bilateral, pheochromocytoma benign																	X									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma						X																	X			3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma malignant, metastatic, brain																										1
Pars distalis, adenoma			X			X	X			X					X		X	X				X	X			14
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, adenoma						X																				4
Follicular cell, adenoma							X		X																	3
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	268	275	354	498	498	527	557	568	618	626	631	631	632	632	632	638	638	652	655	660	600	661	611	663	670	673	677
Carcass ID Number	05044	04644	05244	04643	04491	04553	05225	04895	04444	04473	04492	04563	04455	05334	05445	04663	04655	05133	05564	04433	04422	05122	05611	04885	04882	04435	04494
Genital System																											
Coagulating gland																										+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																											
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X					X	X	X	X	X	X	X	X	X		X				X
Interstitial cell, adenoma							X		X															X		X	
Hematopoietic System																											
Blood	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal, carcinoma, metastatic, kidney																											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	M
Integumentary System																											
Mammary gland	M	M	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Fibroadenoma																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma, multiple																											
Papilloma squamous																											
Subcutaneous tissue, fibroma																											
Subcutaneous tissue, fibrous histiocytoma	X	X																									
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																										X	
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma malignant													X														
Peripheral nerve																								+			
Spinal cord																								+			
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										X	
Fibrous histiocytoma, metastatic, skin	X																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 7	6 8 7	6 9 0	6 9 1	6 9 8	7 0 1	7 0 7	7 1 1	7 1 3	7 1 3	7 1 5	7 1 5	7 1 5	7 1 9	7 2 6	7 2 6	7 2 7	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	0 4 5 4	0 4 7 5	0 5 4 2	0 4 8 4	0 4 3 1	0 5 2 3	0 5 4 3	0 5 3 5	0 5 3 3	0 5 1 1	0 5 6 2	0 5 3 1	0 5 5 1	0 5 5 2	0 5 0 2	0 4 5 1	0 5 2 1	0 5 4 1	0 5 3 2	0 4 3 2	0 4 4 1	0 4 6 1	0 5 1 5	0 5 5 3	0 5 5 5	Total Tissues/ Tumors
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Penis										+	+															2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinoma													X													2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Bilateral, interstitial cell, adenoma	X	X	X	X	X			X	X		X	X	X			X	X		X	X		X		X	X	31
Interstitial cell, adenoma							X			X				X	X			X			X					10
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	M	M	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	41
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Renal, carcinoma, metastatic, kidney																						X				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	M	+	39
Fibroadenoma	X																				X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Keratoacanthoma, multiple										X																1
Papilloma squamous																		X								1
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, fibrous histiocytoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Ependymoma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																										1
Fibrous histiocytoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	268	275	354	498	498	527	557	568	618	626	631	631	632	632	638	638	652	655	660	600	661	661	663	670	673	677
Carcass ID Number	05044	04644	05244	04443	04491	04553	05225	04295	04444	04473	04492	05463	04545	05333	04545	04663	04661	05133	05564	04433	04442	05122	05561	04485	04482	04394
Special Senses System																										
Ear																										
Fibrosarcoma																										
Eye										+	+			+	+		+							+		+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X	X	X		X	X	X	X			X				X	X		X			X	
Mesothelioma malignant																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	6 8 4	6 8 7	6 8 7	6 9 0	6 9 1	6 9 8	7 0 1	7 0 7	7 1 1	7 1 3	7 1 3	7 1 5	7 1 5	7 1 5	7 1 9	7 2 6	7 2 6	7 2 7	7 2 9	7 3 0	7 3 0	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	0 4 5 4	0 4 7 5	0 5 4 2	0 4 8 4	0 4 1 1	0 5 2 3	0 5 4 3	0 5 3 5	0 5 0 3	0 5 1 1	0 5 6 2	0 5 3 1	0 5 5 1	0 5 5 2	0 5 0 2	0 4 5 1	0 5 2 1	0 5 4 1	0 5 3 2	0 4 3 2	0 4 4 1	0 4 6 1	0 5 1 5	0 5 5 3	0 5 5 5	Total Tissues/ Tumors
Special Senses System																										
Ear			+																							1
Fibrosarcoma			X																							1
Eye				+		+													+							10
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Renal tubule, adenoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leukemia mononuclear	X					X						X	X	X				X	X	X	X	X		X	X	25
Mesothelioma malignant																						X				1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	14/52 (27%)	17/51 (33%)	14/51 (27%)	6/52 (12%)
Adjusted rates[b]	45.7%	52.7%	45.7%	31.8%
Terminal rates[c]	9/25 (36%)	3/17 (18%)	7/22 (32%)	0/7 (0%)
First incidence (days)	621	613	618	661
Life table tests[d]	P=0.232N	P=0.168	P=0.503	P=0.501N
Logistic regression tests[d]	P=0.016N	P=0.302	P=0.575	P=0.072N
Cochran-Armitage test[d]	P=0.010N			
Fisher exact test[d]		P=0.311	P=0.564	P=0.040N
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rates	14/52 (27%)	18/51 (35%)	16/51 (31%)	6/52 (12%)
Adjusted rates	45.7%	56.1%	53.0%	31.8%
Terminal rates	9/25 (36%)	4/17 (24%)	9/22 (41%)	0/7 (0%)
First incidence (days)	621	613	618	661
Life table tests	P=0.246N	P=0.118	P=0.333	P=0.501N
Logistic regression tests	P=0.014N	P=0.230	P=0.392	P=0.072N
Cochran-Armitage test	P=0.008N			
Fisher exact test		P=0.241	P=0.390	P=0.040N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	0/52 (0%)	3/51 (6%)	0/51 (0%)	0/52 (0%)
Adjusted rates	0.0%	12.5%	0.0%	0.0%
Terminal rates	0/25 (0%)	1/17 (6%)	0/22 (0%)	0/7 (0%)
First incidence (days)	–[e]	666	–	–
Life table tests	P=0.353N	P=0.097	–	–
Logistic regression tests	P=0.273N	P=0.115	–	–
Cochran-Armitage test	P=0.254N			
Fisher exact test		P=0.118	–	–
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/52 (4%)	3/51 (6%)	0/51 (0%)	1/52 (2%)
Adjusted rates	8.0%	12.5%	0.0%	3.7%
Terminal rates	2/25 (8%)	1/17 (6%)	0/22 (0%)	0/7 (0%)
First incidence (days)	729 (T)	666	–	673
Life table tests	P=0.498N	P=0.388	P=0.266N	P=0.695
Logistic regression tests	P=0.332N	P=0.478	P=0.266N	P=0.581N
Cochran-Armitage test	P=0.289N			
Fisher exact test		P=0.491	P=0.252N	P=0.500N
Pancreatic Islets: Adenoma				
Overall rates	0/52 (0%)	3/50 (6%)	4/51 (8%)	3/51 (6%)
Adjusted rates	0.0%	11.5%	15.4%	20.5%
Terminal rates	0/25 (0%)	1/17 (6%)	2/22 (9%)	1/7 (14%)
First incidence (days)	–	613	701	631
Life table tests	P=0.100	P=0.102	P=0.062	P=0.053
Logistic regression tests	P=0.236	P=0.115	P=0.060	P=0.107
Cochran-Armitage test	P=0.274			
Fisher exact test		P=0.114	P=0.057	P=0.118

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	0/52 (0%)	3/50 (6%)	4/51 (8%)	4/51 (8%)
Adjusted rates	0.0%	11.5%	15.4%	23.3%
Terminal rates	0/25 (0%)	1/17 (6%)	2/22 (9%)	1/7 (14%)
First incidence (days)	–	613	701	631
Life table tests	P=0.036	P=0.102	P=0.062	P=0.026
Logistic regression tests	P=0.115	P=0.115	P=0.060	P=0.055
Cochran-Armitage test	P=0.139			
Fisher exact test		P=0.114	P=0.057	P=0.057
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	13/52 (25%)	12/49 (24%)	15/51 (29%)	15/50 (30%)
Adjusted rates	39.0%	46.4%	43.2%	65.5%
Terminal rates	7/25 (28%)	6/17 (35%)	6/22 (27%)	2/7 (29%)
First incidence (days)	547	613	417	618
Life table tests	P=0.028	P=0.464	P=0.355	P=0.041
Logistic regression tests	P=0.267	P=0.566N	P=0.394	P=0.312
Cochran-Armitage test	P=0.300			
Fisher exact test		P=0.568N	P=0.389	P=0.365
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	13/52 (25%)	12/49 (24%)	16/51 (31%)	15/50 (30%)
Adjusted rates	39.0%	46.4%	44.5%	65.5%
Terminal rates	7/25 (28%)	6/17 (35%)	6/22 (27%)	2/7 (29%)
First incidence (days)	547	613	417	618
Life table tests	P=0.030	P=0.464	P=0.285	P=0.041
Logistic regression tests	P=0.276	P=0.566N	P=0.311	P=0.312
Cochran-Armitage test	P=0.304			
Fisher exact test		P=0.568N	P=0.309	P=0.365
Preputial Gland: Adenoma				
Overall rates	3/52 (6%)	1/51 (2%)	1/51 (2%)	0/52 (0%)
Adjusted rates	12.0%	3.8%	4.5%	0.0%
Terminal rates	3/25 (12%)	0/17 (0%)	1/22 (5%)	0/7 (0%)
First incidence (days)	729 (T)	694	729 (T)	–
Life table tests	P=0.252N	P=0.420N	P=0.350N	P=0.411N
Logistic regression tests	P=0.164N	P=0.335N	P=0.350N	P=0.411N
Cochran-Armitage test	P=0.116N			
Fisher exact test		P=0.316N	P=0.316N	P=0.121N
Preputial Gland: Carcinoma				
Overall rates	2/52 (4%)	2/51 (4%)	4/51 (8%)	2/52 (4%)
Adjusted rates	4.9%	5.0%	14.9%	9.9%
Terminal rates	0/25 (0%)	0/17 (0%)	2/22 (9%)	0/7 (0%)
First incidence (days)	571	613	659	655
Life table tests	P=0.499	P=0.666N	P=0.322	P=0.646
Logistic regression tests	P=0.594N	P=0.688	P=0.330	P=0.693N
Cochran-Armitage test	P=0.588N			
Fisher exact test		P=0.684	P=0.330	P=0.691N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rates	5/52 (10%)	3/51 (6%)	5/51 (10%)	2/52 (4%)
Adjusted rates	16.3%	8.6%	19.2%	9.9%
Terminal rates	3/25 (12%)	0/17 (0%)	3/22 (14%)	0/7 (0%)
First incidence (days)	571	613	659	655
Life table tests	P=0.466N	P=0.424N	P=0.580	P=0.492N
Logistic regression tests	P=0.244N	P=0.367N	P=0.623	P=0.230N
Cochran-Armitage test	P=0.226N			
Fisher exact test		P=0.369N	P=0.617	P=0.218N
Skin: Basal Cell Adenoma or Basal Cell Carcinoma				
Overall rates	1/52 (2%)	0/51 (0%)	3/51 (6%)	0/52 (0%)
Adjusted rates	4.0%	0.0%	11.1%	0.0%
Terminal rates	1/25 (4%)	0/17 (0%)	1/22 (5%)	0/7 (0%)
First incidence (days)	729 (T)	–	684	–
Life table tests	P=0.659N	P=0.577N	P=0.291	P=0.752N
Logistic regression tests	P=0.518N	P=0.577N	P=0.300	P=0.752N
Cochran-Armitage test	P=0.446N			
Fisher exact test		P=0.505N	P=0.301	P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma or Basal Cell Carcinoma				
Overall rates	3/52 (6%)	1/51 (2%)	4/51 (8%)	2/52 (4%)
Adjusted rates	10.7%	5.9%	13.6%	18.0%
Terminal rates	1/25 (4%)	1/17 (6%)	1/22 (5%)	0/7 (0%)
First incidence (days)	691	729 (T)	635	713
Life table tests	P=0.396	P=0.403N	P=0.494	P=0.567
Logistic regression tests	P=0.599	P=0.320N	P=0.493	P=0.617N
Cochran-Armitage test	P=0.556N			
Fisher exact test		P=0.316N	P=0.489	P=0.500N
Skin (Subcutaneous Tissue): Neurofibrosarcoma or Fibrosarcoma				
Overall rates	3/52 (6%)	2/51 (4%)	0/51 (0%)	0/52 (0%)
Adjusted rates	8.8%	6.3%	0.0%	0.0%
Terminal rates	1/25 (4%)	0/17 (0%)	0/22 (0%)	0/7 (0%)
First incidence (days)	495	333	–	–
Life table tests	P=0.098N	P=0.553N	P=0.135N	P=0.207N
Logistic regression tests	P=0.073N	P=0.509N	P=0.128N	P=0.119N
Cochran-Armitage test	P=0.072N			
Fisher exact test		P=0.509N	P=0.125N	P=0.121N
Skin (Subcutaneous Tissue): Fibroma, Neurofibrosarcoma, or Fibrosarcoma				
Overall rates	3/52 (6%)	2/51 (4%)	1/51 (2%)	1/52 (2%)
Adjusted rates	8.8%	6.3%	2.6%	6.3%
Terminal rates	1/25 (4%)	0/17 (0%)	0/22 (0%)	0/7 (0%)
First incidence (days)	495	333	618	713
Life table tests	P=0.343N	P=0.553N	P=0.322N	P=0.479N
Logistic regression tests	P=0.260N	P=0.509N	P=0.323N	P=0.305N
Cochran-Armitage test	P=0.261N			
Fisher exact test		P=0.509N	P=0.316N	P=0.309N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Testes: Adenoma				
Overall rates	46/52 (88%)	42/51 (82%)	42/51 (82%)	41/52 (79%)
Adjusted rates	100.0%	97.7%	100.0%	97.5%
Terminal rates	25/25 (100%)	16/17 (94%)	22/22 (100%)	6/7 (86%)
First incidence (days)	456	532	481	498
Life table tests	P=0.005	P=0.299	P=0.502N	P=0.010
Logistic regression tests	P=0.154N	P=0.231N	P=0.236N	P=0.134N
Cochran-Armitage test	P=0.174N			
Fisher exact test		P=0.275N	P=0.275N	P=0.144N
Thyroid Gland (C-cell): Adenoma				
Overall rates	6/52 (12%)	8/48 (17%)	7/51 (14%)	4/51 (8%)
Adjusted rates	19.6%	29.7%	22.4%	12.9%
Terminal rates	4/25 (16%)	3/17 (18%)	3/22 (14%)	0/7 (0%)
First incidence (days)	495	451	519	631
Life table tests	P=0.507N	P=0.250	P=0.447	P=0.583
Logistic regression tests	P=0.204N	P=0.330	P=0.487	P=0.387N
Cochran-Armitage test	P=0.200N			
Fisher exact test		P=0.326	P=0.485	P=0.383N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	1/52 (2%)	1/48 (2%)	1/51 (2%)	3/51 (6%)
Adjusted rates	3.0%	3.3%	2.6%	12.7%
Terminal rates	0/25 (0%)	0/17 (0%)	0/22 (0%)	0/7 (0%)
First incidence (days)	673	682	621	527
Life table tests	P=0.119	P=0.757	P=0.757	P=0.227
Logistic regression tests	P=0.162	P=0.748	P=0.756	P=0.298
Cochran-Armitage test	P=0.160			
Fisher exact test		P=0.732	P=0.748	P=0.301
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	1/52 (2%)	3/48 (6%)	1/51 (2%)	3/51 (6%)
Adjusted rates	3.0%	11.0%	2.6%	12.7%
Terminal rates	0/25 (0%)	0/17 (0%)	0/22 (0%)	0/7 (0%)
First incidence (days)	673	682	621	527
Life table tests	P=0.253	P=0.285	P=0.757	P=0.227
Logistic regression tests	P=0.346	P=0.282	P=0.756	P=0.298
Cochran-Armitage test	P=0.350			
Fisher exact test		P=0.279	P=0.748	P=0.301
All Organs: Mononuclear Cell Leukemia				
Overall rates	32/52 (62%)	31/51 (61%)	30/51 (59%)	25/52 (48%)
Adjusted rates	79.0%	90.5%	77.1%	93.6%
Terminal rates	17/25 (68%)	14/17 (82%)	14/22 (64%)	6/7 (86%)
First incidence (days)	526	532	481	498
Life table tests	P=0.126	P=0.240	P=0.557	P=0.130
Logistic regression tests	P=0.089N	P=0.549N	P=0.445N	P=0.132N
Cochran-Armitage test	P=0.074N			
Fisher exact test		P=0.549N	P=0.468N	P=0.119N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
All Organs: Benign Neoplasms				
Overall rates	49/52 (94%)	46/51 (90%)	48/51 (94%)	47/52 (90%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	25/25 (100%)	17/17 (100%)	22/22 (100%)	7/7 (100%)
First incidence (days)	456	346	417	498
Life table tests	P=0.002	P=0.254	P=0.437	P=0.004
Logistic regression tests	P=0.391N	P=0.373N	P=0.598N	P=0.375N
Cochran-Armitage test	P=0.392N			
Fisher exact test		P=0.347N	P=0.652N	P=0.358N
All Organs: Malignant Neoplasms				
Overall rates	38/52 (73%)	38/51 (75%)	34/51 (67%)	30/52 (58%)
Adjusted rates	83.7%	94.7%	83.8%	94.5%
Terminal rates	18/25 (72%)	15/17 (88%)	16/22 (73%)	6/7 (86%)
First incidence (days)	269	333	481	268
Life table tests	P=0.153	P=0.194	P=0.462N	P=0.152
Logistic regression tests	P=0.033N	P=0.522	P=0.295N	P=0.072N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.524	P=0.311N	P=0.074N
All Organs: Benign or Malignant Neoplasms				
Overall rates	51/52 (98%)	48/51 (94%)	49/51 (96%)	51/52 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	25/25 (100%)	17/17 (100%)	22/22 (100%)	7/7 (100%)
First incidence (days)	269	333	417	268
Life table tests	P=0.001	P=0.261	P=0.489	P=0.003
Logistic regression tests	P=0.448	P=0.247N	P=0.169N	P=0.697N
Cochran-Armitage test	P=0.415			
Fisher exact test		P=0.301N	P=0.493N	P=0.752N

(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, epididymis, heart, kidney, larynx, liver, lung, nose, 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 control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
2,4-Dichlorophenol	1/49	0/49	1/49
5,5-Diphenylhydantoin	3/50	1/50	4/50
Ethylene thiourea	2/48	1/48	3/48
Polybrominated biphenyls (Firemaster FF-1®)	4/49	3/49	7/49
Manganese (II) sulfate monohydrate	0/52	0/52	0/52
Triamterene	2/50	0/50	2/50
Overall Historical Incidence			
Total	38/989 (3.8%)	11/989 (1.1%)	49/989 (5.0%)
Standard deviation	3.4%	1.7%	3.8%
Range	0%-12%	0%-6%	0%-14%

[a] Data as of 16 December 1991

TABLE A4b
Historical Incidence of Adrenal Medulla Pheochromocytomas in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Benign Pheochromocytoma	Malignant Pheochromocytoma	Benign or Malignant Pheochromocytoma[b]
Historical Incidence at Battelle Columbus Laboratories			
2,4-Dichlorophenol	21/50	0/50	22/50
5,5-Diphenylhydantoin	19/50	0/50	19/50
Ethylene thiourea	22/50	2/50	23/50
Polybrominated biphenyls (Firemaster FF-1®)	11/49	1/49	12/49
Manganese (II) sulfate monohydrate	14/52	1/52	14/52
Triamterene	9/50	1/50	10/50
Overall Historical Incidence			
Total	354/988 (35.8%)	44/988 (4.5%)	380/988 (38.5%)
Standard deviation	11.3%	5.2%	10.5%
Range	14%-63%	0%-20%	20%-63%

[a] Data as of 16 December 1991
[b] Includes data for one complex pheochromocytoma

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	8	10	10	10
15-Month interim evaluation	10	9	9	8
Early deaths				
Moribund	21	24	24	38
Natural deaths	6	10	5	7
Survivors				
Died last week of study			1	
Terminal sacrifice	25	17	21	7
Animals examined microscopically	70	70	70	70
9-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(8)	(1)		(10)
Parasite metazoan		1 (100%)		
Liver	(8)	(1)	(1)	(10)
Basophilic focus	1 (13%)			
Stomach, forestomach	(8)	(3)	(1)	(10)
Diverticulum		1 (33%)		
Cardiovascular System				
Heart	(8)	(1)		(10)
Degeneration, chronic	8 (100%)			6 (60%)
Endocrine System				
Pituitary gland	(7)	(1)		(10)
Pars distalis, hyperplasia	1 (14%)			1 (10%)
General Body System				
None				
Genital System				
Preputial gland	(8)	(1)		(10)
Hyperplasia	1 (13%)			
Inflammation, chronic	1 (13%)			
Inflammation, chronic active	3 (38%)			3 (30%)
Duct, ectasia	1 (13%)			
Prostate	(8)	(1)		(9)
Inflammation, acute				2 (22%)
Seminal vesicle	(8)	(1)		(10)
Hyperplasia				1 (10%)
Testes	(8)	(1)		(10)
Interstitial cell, hyperplasia	1 (13%)			3 (30%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
9-Month Interim Evaluation (continued)				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(8)	(10)	(10)	(10)
Nephropathy, chronic	8 (100%)	10 (100%)	10 (100%)	10 (100%)
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)			(8)
Parasite metazoan	1 (10%)			
Liver	(10)	(1)		(8)
Basophilic focus	1 (10%)	1 (100%)		1 (13%)
Clear cell focus		1 (100%)		
Hepatodiaphragmatic nodule		1 (100%)		
Inflammation, chronic		1 (100%)		1 (13%)
Necrosis, coagulative	1 (10%)			1 (13%)
Mesentery	(2)			
Inflammation, chronic active	2 (100%)			
Pancreas	(10)			(8)
Acinus, atrophy	7 (70%)			3 (38%)
Tooth	(10)			(8)
Inflammation, chronic active	1 (10%)			
Cardiovascular System				
Heart	(10)			(8)
Cardiomyopathy, chronic	10 (100%)			6 (75%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
15-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal gland, cortex	(10)			(8)
Atypical cells				1 (13%)
Hyperplasia	1 (10%)			
Pituitary gland	(10)			(8)
Pars distalis, cyst	3 (30%)			2 (25%)
Pars distalis, hyperplasia	3 (30%)			2 (25%)
Pars distalis, hypertrophy	1 (10%)			
Pars intermedia, cyst				3 (38%)
Thyroid gland	(10)			(8)
C-cell, hyperplasia	1 (10%)			
General Body System				
None				
Genital System				
Preputial gland	(10)	(1)	(1)	(8)
Hyperplasia				1 (13%)
Inflammation, chronic active	5 (50%)	1 (100%)		5 (63%)
Prostate	(10)			(8)
Cyst	1 (10%)			
Inflammation, chronic active	3 (30%)			6 (75%)
Testes	(10)	(2)		(8)
Interstitial cell, hyperplasia	9 (90%)			8 (100%)
Hematopoietic System				
Lymph node, mandibular	(10)			(8)
Cyst	1 (10%)			
Hyperplasia, plasma cell	1 (10%)			
Integumentary System				
Mammary gland	(7)			(5)
Hyperplasia, cystic	7 (100%)			5 (100%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Nose	(10)			(8)
Fungus	1 (10%)			
Inflammation, chronic active	1 (10%)			
Nasolacrimal duct, inflammation, suppurative	1 (10%)			1 (13%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
15-Month Interim Evaluation (continued)				
Special Senses System				
None				
Urinary System				
Kidney	(10)	(9)	(9)	(8)
Nephropathy, chronic	10 (100%)	9 (100%)	9 (100%)	8 (100%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(52)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Parasite metazoan				1 (2%)
Intestine large, colon	(52)	(51)	(50)	(52)
Inflammation, chronic active				1 (2%)
Mineralization		1 (2%)		
Parasite metazoan	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Intestine large, rectum	(52)	(51)	(51)	(52)
Inflammation, chronic active		1 (2%)		
Parasite metazoan	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Thrombus		1 (2%)		
Intestine small, ileum	(52)	(50)	(51)	(51)
Inflammation, chronic active			1 (2%)	
Lymphoid tissue, hyperplasia			1 (2%)	
Liver	(52)	(51)	(51)	(52)
Basophilic focus	10 (19%)	8 (16%)	10 (20%)	8 (15%)
Clear cell focus	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Degeneration, cystic	16 (31%)	19 (37%)	19 (37%)	12 (23%)
Hepatodiaphragmatic nodule	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Hyperplasia	2 (4%)	2 (4%)		2 (4%)
Inflammation, chronic	26 (50%)	29 (57%)	25 (49%)	30 (58%)
Leukocytosis		2 (4%)	2 (4%)	
Necrosis, coagulative	3 (6%)	4 (8%)	4 (8%)	
Thrombus			1 (2%)	1 (2%)
Vacuolization cytoplasmic	23 (44%)	23 (45%)	24 (47%)	21 (40%)
Bile duct, hyperplasia	48 (92%)	50 (98%)	48 (94%)	47 (90%)
Hepatocyte, atrophy			1 (2%)	
Mesentery	(6)	(9)	(5)	(6)
Inflammation, necrotizing	3 (50%)	6 (67%)	5 (100%)	5 (83%)
Pancreas	(52)	(50)	(51)	(51)
Cyst	2 (4%)			1 (2%)
Ectopic tissue		1 (2%)		
Infiltration cellular, lipocyte	20 (38%)	13 (26%)	25 (49%)	14 (27%)
Acinus, atrophy	19 (37%)	28 (56%)	18 (35%)	19 (37%)
Acinus, hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Perivascular, inflammation, chronic active	6 (12%)	2 (4%)	2 (4%)	3 (6%)
Salivary glands	(52)	(47)	(51)	(51)
Sublingual gland, hyperplasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(52)	(51)	(51)	(52)
Acanthosis	19 (37%)	12 (24%)	11 (22%)	11 (21%)
Hyperkeratosis	3 (6%)	3 (6%)	6 (12%)	2 (4%)
Inflammation, chronic active	11 (21%)	8 (16%)	8 (16%)	8 (15%)
Mineralization	2 (4%)	4 (8%)	3 (6%)	2 (4%)
Stomach, glandular	(52)	(51)	(51)	(52)
Erosion		2 (4%)	1 (2%)	
Inflammation, chronic active	4 (8%)	8 (16%)	8 (16%)	4 (8%)
Mineralization	8 (15%)	13 (25%)	9 (18%)	23 (44%)
Tooth	(51)	(50)	(51)	(51)
Caries				1 (2%)
Inflammation, chronic active			1 (2%)	1 (2%)
Cardiovascular System				
Blood vessel	(52)	(51)	(51)	(52)
Inflammation, chronic active		1 (2%)	1 (2%)	1 (2%)
Mineralization	4 (8%)	10 (20%)	6 (12%)	17 (33%)
Thrombus			1 (2%)	1 (2%)
Heart	(52)	(51)	(51)	(52)
Cardiomyopathy, chronic	47 (90%)	48 (94%)	51 (100%)	46 (88%)
Mineralization	4 (8%)	8 (16%)	5 (10%)	9 (17%)
Atrium, thrombus	5 (10%)	5 (10%)	5 (10%)	
Valve, inflammation, chronic active		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(52)	(51)	(51)	(52)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Degeneration, fatty	33 (63%)	27 (53%)	32 (63%)	28 (54%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	20 (38%)	14 (27%)	17 (33%)	18 (35%)
Hypertrophy	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Necrosis, coagulative	1 (2%)		2 (4%)	
Adrenal gland, medulla	(52)	(51)	(51)	(52)
Atrophy			1 (2%)	
Hyperplasia	28 (54%)	23 (45%)	31 (61%)	27 (52%)
Islets, pancreatic	(52)	(50)	(51)	(51)
Hyperplasia		2 (4%)	2 (4%)	3 (6%)
Parathyroid gland	(51)	(46)	(49)	(50)
Hyperplasia	14 (27%)	14 (30%)	12 (24%)	23 (46%)
Pituitary gland	(52)	(49)	(51)	(50)
Mineralization				1 (2%)
Craniopharyngeal duct, cyst		1 (2%)	1 (2%)	2 (4%)
Pars distalis, cyst	5 (10%)	7 (14%)	2 (4%)	6 (12%)
Pars distalis, hyperplasia	17 (33%)	15 (31%)	18 (35%)	10 (20%)
Pars intermedia, cyst		2 (4%)	1 (2%)	3 (6%)
Pars nervosa, cyst		1 (2%)		
Thyroid gland	(52)	(48)	(51)	(51)
C-cell, hyperplasia	18 (35%)	12 (25%)	15 (29%)	6 (12%)
Follicle, cyst multilocular	1 (2%)		1 (2%)	1 (2%)
Follicular cell, mineralization	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
General Body System				
None				
Genital System				
Coagulating gland	(1)	(3)	(1)	(1)
Inflammation, chronic active	1 (100%)	2 (67%)	1 (100%)	1 (100%)
Epididymis	(52)	(51)	(51)	(52)
Inflammation, chronic active				1 (2%)
Mineralization			1 (2%)	1 (2%)
Preputial gland	(52)	(51)	(51)	(52)
Hyperplasia	2 (4%)	3 (6%)		1 (2%)
Inflammation, chronic active	44 (85%)	49 (96%)	45 (88%)	45 (87%)
Prostate	(52)	(51)	(51)	(52)
Cyst		2 (4%)	1 (2%)	
Inflammation, chronic active	37 (71%)	38 (75%)	44 (86%)	42 (81%)
Mineralization	1 (2%)	1 (2%)		
Thrombus				1 (2%)
Epithelium, hyperplasia	1 (2%)			
Seminal vesicle	(52)	(51)	(51)	(52)
Inflammation, chronic active	1 (2%)		2 (4%)	
Mineralization				2 (4%)
Testes	(52)	(51)	(51)	(52)
Mineralization	25 (48%)	31 (61%)	22 (43%)	29 (56%)
Necrosis, coagulative				1 (2%)
Interstitial cell, hyperplasia	10 (19%)	15 (29%)	10 (20%)	16 (31%)
Seminiferous tubule, atrophy	3 (6%)	5 (10%)	3 (6%)	8 (15%)
Hematopoietic System				
Blood	(46)	(42)	(44)	(41)
Leukocytosis		1 (2%)	2 (5%)	
Bone marrow	(52)	(51)	(51)	(52)
Femoral, atrophy			2 (4%)	
Femoral, myelofibrosis		2 (4%)		
Lymph node	(52)	(51)	(51)	(52)
Mediastinal, hyperplasia, plasma cell			1 (2%)	
Pancreatic, inflammation, chronic active				1 (2%)
Renal, hyperplasia, plasma cell		1 (2%)		
Lymph node, mandibular	(51)	(47)	(51)	(50)
Cyst	4 (8%)	7 (15%)	3 (6%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)		3 (6%)	
Lymph node, mesenteric	(51)	(50)	(51)	(51)
Cyst	1 (2%)		1 (2%)	
Inflammation, chronic active		1 (2%)		1 (2%)
Spleen	(52)	(51)	(51)	(52)
Fibrosis	4 (8%)	6 (12%)	7 (14%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	4 (8%)	1 (2%)
Infiltration cellular, lipocyte	1 (2%)	1 (2%)		
Necrosis, coagulative		1 (2%)	1 (2%)	
Thrombus				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Thymus	(49)	(47)	(49)	(45)
Cyst				1 (2%)
Ectopic parathyroid gland	2 (4%)	1 (2%)		
Ectopic thyroid				1 (2%)
Integumentary System				
Mammary gland	(45)	(38)	(36)	(39)
Hyperplasia, cystic	37 (82%)	38 (100%)	36 (100%)	34 (87%)
Skin	(49)	(51)	(50)	(52)
Acanthosis	2 (4%)	1 (2%)		
Alopecia		1 (2%)	1 (2%)	
Cyst epithelial inclusion		1 (2%)		
Hyperkeratosis	1 (2%)			2 (4%)
Inflammation, chronic active	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Mineralization			1 (2%)	
Ulcer	1 (2%)			
Musculoskeletal System				
Bone	(52)	(51)	(51)	(52)
Cranium, fibrous osteodystrophy	12 (23%)	13 (25%)	11 (22%)	23 (44%)
Femur, fibrous osteodystrophy	12 (23%)	14 (27%)	12 (24%)	24 (46%)
Nervous System				
Brain	(52)	(50)	(51)	(52)
Compression	4 (8%)	4 (8%)	7 (14%)	4 (8%)
Hydrocephalus	4 (8%)	5 (10%)	8 (16%)	5 (10%)
Necrosis	1 (2%)		1 (2%)	
Spinal cord	(1)	(2)		(1)
White matter, degeneration		1 (50%)		1 (100%)
Respiratory System				
Lung	(52)	(51)	(51)	(52)
Hemorrhage				1 (2%)
Infiltration cellular, histiocyte	12 (23%)	18 (35%)	9 (18%)	11 (21%)
Inflammation, chronic active	5 (10%)	9 (18%)	9 (18%)	8 (15%)
Leukocytosis		1 (2%)	2 (4%)	
Metaplasia, osseous	1 (2%)	4 (8%)	2 (4%)	3 (6%)
Mineralization	4 (8%)	6 (12%)	6 (12%)	10 (19%)
Thrombus	1 (2%)	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)	5 (10%)	1 (2%)
Mediastinum, inflammation, chronic active		1 (2%)		
Nose	(52)	(50)	(51)	(52)
Fungus	1 (2%)	4 (8%)		1 (2%)
Inflammation, chronic active	6 (12%)	9 (18%)	7 (14%)	11 (21%)
Nasolacrimal duct, inflammation, suppurative	17 (33%)	16 (32%)	18 (35%)	16 (31%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Special Senses System				
Eye	(3)	(2)	(6)	(10)
Anterior chamber, inflammation, suppurative				1 (10%)
Cornea, inflammation, chronic active	1 (33%)	1 (50%)	3 (50%)	5 (50%)
Cornea, mineralization	1 (33%)		3 (50%)	6 (60%)
Lens, cataract	1 (33%)	1 (50%)	2 (33%)	2 (20%)
Retina, atrophy	1 (33%)	1 (50%)	2 (33%)	2 (20%)
Harderian gland	(52)	(51)	(51)	(52)
Inflammation, chronic active		1 (2%)		
Urinary System				
Kidney	(52)	(50)	(51)	(52)
Hydronephrosis	1 (2%)			
Infarct			1 (2%)	
Nephropathy, chronic	50 (96%)	49 (98%)	51 (100%)	50 (96%)
Thrombus			1 (2%)	1 (2%)
Glomerulus, inflammation, chronic active		1 (2%)		
Renal tubule, hyperplasia	1 (2%)	3 (6%)		2 (4%)
Renal tubule, hyperplasia, oncocytic		1 (2%)		
Urinary bladder	(52)	(50)	(51)	(52)
Infiltration cellular, histiocyte			1 (2%)	
Inflammation, chronic active	1 (2%)			
Transitional epithelium, hyperplasia	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 FEED STUDY OF MANGANESE (II) SULFATE MONOHYDRATE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-month interim evaluation[b]	10	10	10	10
15-month interim evaluation[c]	10	10	9	10
Early deaths				
Accidental deaths			1	
Moribund	6	11	6	11
Natural deaths	7	2	2	1
Survivors				
Terminal sacrifice	37	37	42	36
Missexed				2
Animals examined microscopically	70	61	62	68
15-Month Interim Evaluation				
Endocrine System				
Pituitary gland	(10)	(1)		(10)
Pars distalis, adenoma				2 (20%)
Genital System				
Uterus	(10)	(1)	(2)	(10)
Polyp stromal			2 (100%)	
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(48)
Adenocarcinoma				1 (2%)
Liver	(50)	(50)	(51)	(48)
Hepatocellular carcinoma		1 (2%)		
Hepatocellular adenoma			1 (2%)	
Mesentery	(3)	(3)	(3)	(2)
Liposarcoma			1 (33%)	
Pancreas	(50)	(49)	(50)	(48)
Salivary glands	(50)	(50)	(50)	(48)
Stomach, forestomach	(50)	(50)	(50)	(48)
Papilloma squamous			2 (4%)	
Stomach, glandular	(50)	(50)	(50)	(48)
Tongue		(1)		
Papilloma squamous		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(51)	(48)
Schwannoma malignant, metastatic, lung		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(51)	(48)
Adenoma	1 (2%)	1 (2%)		
Carcinoma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal gland, medulla	(50)	(50)	(51)	(48)
Pheochromocytoma complex	1 (2%)			
Pheochromocytoma benign	1 (2%)		4 (8%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(48)
Adenoma			1 (2%)	
Parathyroid gland	(46)	(46)	(46)	(46)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Pituitary gland	(50)	(50)	(51)	(47)
Pars distalis, adenoma	22 (44%)	17 (34%)	19 (37%)	20 (43%)
Pars distalis, adenoma, multiple	1 (2%)			
Pars distalis, carcinoma		1 (2%)		2 (4%)
Thyroid gland	(50)	(50)	(50)	(48)
Bilateral, C-cell, adenoma				2 (4%)
C-cell, adenoma	8 (16%)	6 (12%)	6 (12%)	6 (13%)
C-cell, adenoma, multiple		1 (2%)		
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(49)	(49)	(47)	(47)
Adenoma	5 (10%)	1 (2%)	6 (13%)	2 (4%)
Carcinoma		1 (2%)	1 (2%)	
Ovary	(50)	(50)	(51)	(48)
Granulosa cell tumor malignant			1 (2%)	
Granulosa cell tumor benign		1 (2%)		1 (2%)
Granulosa-theca tumor benign				1 (2%)
Uterus	(50)	(50)	(51)	(48)
Hemangiosarcoma				1 (2%)
Leiomyoma				1 (2%)
Polyp stromal	13 (26%)	7 (14%)	6 (12%)	7 (15%)
Sarcoma stromal		1 (2%)		
Hematopoietic System				
Blood	(41)	(48)	(48)	(48)
Bone marrow	(50)	(50)	(51)	(48)
Lymph node	(50)	(50)	(51)	(48)
Deep cervical, carcinoma, metastatic, thyroid gland			1 (2%)	
Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle				1 (2%)
Lymph node, mandibular	(50)	(50)	(50)	(47)
Lymph node, mesenteric	(49)	(50)	(51)	(46)
Spleen	(50)	(50)	(51)	(48)
Hemangiosarcoma			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Thymus	(46)	(48)	(47)	(45)
Carcinoma, metastatic			1 (2%)	
Thymoma benign	2 (4%)		1 (2%)	1 (2%)
Integumentary System				
Mammary gland	(48)	(49)	(51)	(46)
Adenocarcinoma		1 (2%)		
Fibroadenoma	15 (31%)	14 (29%)	26 (51%)	11 (24%)
Fibroadenoma, multiple	4 (8%)	2 (4%)		5 (11%)
Skin	(50)	(50)	(51)	(47)
Basal cell adenoma	1 (2%)			
Basal cell carcinoma	1 (2%)			
Basosquamous tumor benign		1 (2%)		
Keratoacanthoma		1 (2%)		
Papilloma squamous		1 (2%)		
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Musculoskeletal System				
Skeletal muscle	(50)	(50)	(51)	(48)
Rhabdomyosarcoma				1 (2%)
Nervous System				
Brain	(50)	(50)	(51)	(48)
Carcinoma, metastatic, pituitary gland				2 (4%)
Granular cell tumor benign				1 (2%)
Oligodendroglioma NOS				1 (2%)
Spinal cord		(1)		
Schwannoma NOS		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(51)	(48)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		2 (4%)
Fibrosarcoma, metastatic, skin		1 (2%)		
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle				1 (2%)
Mediastinum, schwannoma malignant		1 (2%)		
Special Senses System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Urinary System				
Kidney	(50)	(50)	(51)	(48)
Liposarcoma, metastatic, mesentery			1 (2%)	
Renal tubule, adenoma			1 (2%)	
Renal tubule, carcinoma			1 (2%)	
Urinary bladder	(49)	(50)	(51)	(48)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(51)	(48)
Leukemia mononuclear	19 (38%)	21 (42%)	26 (51%)	18 (38%)
Neoplasm Summary				
Total animals with primary neoplasms[d]				
15-Month interim evaluation			2	2
2-Year study	45	47	49	42
Total primary neoplasms				
15-Month interim evaluation			2	2
2-Year study	99	89	106	86
Total animals with benign neoplasms				
15-Month interim evaluation			2	2
2-Year study	40	36	43	36
Total benign neoplasms				
15-Month interim evaluation			2	2
2-Year study	75	56	73	62
Total animals with malignant neoplasms				
2-Year study	24	26	30	22
Total malignant neoplasms				
2-Year study	24	32	33	23
Total animals with metastatic neoplasms				
2-Year study		3	3	3
Total secondary neoplasms				
2-Year study		3	3	4
Total animals with neoplasms uncertain-benign or malignant				
2-Year study		1		1
Total uncertain neoplasms				
2-Year study		1		1

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were observed at any site in any animal at the 9-month interim evaluation.
[c] No neoplasms were observed in the alimentary, cardiovascular, general body, hematopoietic, integumentary, musculoskeletal, nervous, respiratory, special senses, and urinary systems in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm

Number of Days on Study	5 4 7	5 8 5	5 9 9	6 2 0	6 2 4	6 3 8	6 4 2	6 7 5	6 9 0	6 9 4	6 9 4	6 9 9	7 2 8	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
Carcass ID Number	0 6 0 1	0 5 7 2	0 5 8 1	0 5 9 4	0 6 9 3	0 6 0 5	0 6 9 1	0 6 5 4	0 6 1 2	0 6 6 5	0 7 0 5	0 5 7 1	0 5 7 5	0 5 8 3	0 5 8 4	0 5 9 1	0 5 9 2	0 5 9 3	0 5 9 5	0 6 0 2	0 7 0 3	0 6 0 3	0 6 1 1	0 6 1 3	0 6 1 5
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X							
Carcinoma		X																						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex										X														
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X		X			X	X	X		X	X	X						X	X	X
Pars distalis, adenoma, multiple																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma			X				X								X	X								X
C-cell, carcinoma																								
Follicular cell, carcinoma																			X					
General Body System																								
None																								

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 6 2 2	0 6 2 3	0 6 2 5	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 2	0 6 4 3	0 6 4 4	0 6 4 5	0 6 5 2	0 6 5 3	0 6 6 1	0 6 6 3	0 6 6 4	0 6 7 2	0 6 7 5	0 6 8 3	0 6 8 4	0 6 8 5	0 6 9 2	0 6 9 4	0 7 0 1	0 7 0 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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				+																						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X					X	X	X				X			X			X	X		X		22
Pars distalis, adenoma, multiple						X																				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X											X	X				8
C-cell, carcinoma						X																				1
Follicular cell, carcinoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	5 4 7	5 8 5	5 9 9	6 2 0	6 2 4	6 3 8	6 4 2	6 7 5	6 9 0	6 9 4	6 9 4	6 9 9	7 2 8	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
Carcass ID Number	0 6 0 1	0 5 7 2	0 5 8 1	0 5 9 4	0 6 9 3	0 6 0 5	0 6 9 1	0 6 5 4	0 6 1 2	0 6 6 5	0 7 0 5	0 5 7 1	0 5 7 5	0 5 8 3	0 5 8 4	0 5 9 1	0 5 9 2	0 5 9 3	0 5 9 5	0 6 0 2	0 7 0 3	0 6 0 3	0 6 1 1	0 6 1 3	0 6 1 5
Genital System																								
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																			X		X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal										X				X		X	X			X					
Vagina								+																	
Hematopoietic System																									
Blood	M	M	+	M	M	+	+	+	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thymoma benign																				X					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X	X						X							X		X	X			X
Fibroadenoma, multiple										X								X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																							X		
Basal cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye													+												
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																							X		
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 Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 6 2 2	0 6 2 3	0 6 2 5	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 2	0 6 4 3	0 6 4 4	0 6 4 5	0 6 5 2	0 6 5 3	0 6 6 1	0 6 6 3	0 6 6 4	0 6 7 2	0 6 7 5	0 6 8 3	0 6 8 4	0 6 8 5	0 6 9 2	0 6 9 4	0 7 0 1	0 7 0 2	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X						X									5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X		X	X	X							X			X			X					X		13
Vagina																										1
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Thymoma benign																					X					2
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma						X	X							X		X		X	X				X	X		15
Fibroadenoma, multiple					X										X											4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Basal cell carcinoma										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+							+														3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X	X								X				X				X	19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm

Number of Days on Study	3 9 6	4 5 1	4 9 1	5 4 0	5 4 3	5 4 8	5 5 7	5 6 8	6 0 9	6 6 7	6 7 3	7 1 8	7 1 8	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
Carcass ID Number	0 7 3 5	0 7 1 5	0 7 2 3	0 7 9 2	0 7 4 2	0 7 2 2	0 8 0 4	0 7 9 5	0 7 5 1	0 8 4 5	0 7 8 3	0 7 1 1	0 8 3 2	0 7 2 1	0 7 3 2	0 7 3 4	0 7 4 1	0 7 4 3	0 7 4 5	0 7 5 2	0 7 7 9 1	0 8 4 3	0 7 5 3	0 7 5 5	0 7 6 1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																								X	
Mesentery												+												+	
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, lung			X																						
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																					X				
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X	X										X					X		X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
C-cell, adenoma, multiple																									
C-cell, carcinoma														X							X				
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	730	700	700	700	700	700	700	731	711	711	711	711	711	711	711	711	722	722	722	722	722	722	722	722	722	
Carcass ID Number	00762	00763	00764	00765	00771	00772	00774	00781	00784	00794	00801	00803	00805	00811	00812	00813	00814	00815	00821	00822	00823	00824	00834	00835	00844	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
Hepatocellular carcinoma																										1
Mesentery								+																		3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						1
Papilloma squamous																				X						1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Carcinoma, metastatic, thyroid gland																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X			X			X		X		X			X	X			X				X	17
Pars distalis, carcinoma															X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X													X				X		X			X			6
C-cell, adenoma, multiple							X																			1
C-cell, carcinoma																										2
Follicular cell, carcinoma					X																					1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	3 9 6	4 5 1	4 9 1	5 4 0	5 4 3	5 4 8	5 5 7	5 6 8	6 0 9	6 6 7	6 7 3	7 1 8	7 1 8	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
Carcass ID Number	0 7 3 5	0 7 1 5	0 7 2 3	0 7 9 2	0 7 4 2	0 7 2 2	0 8 0 4	0 7 9 5	0 7 5 1	0 8 4 5	0 7 8 3	0 7 1 1	0 8 3 2	0 7 2 1	0 7 3 2	0 7 3 4	0 7 4 1	0 7 4 3	0 7 4 5	0 7 5 2	0 7 7 9 1	0 8 4 3	0 7 5 3	0 7 5 5	0 7 6 1
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal		X											X					X							X
Sarcoma stromal	X																								
Hematopoietic System																									
Blood	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma												X		X		X	X				X			X
Fibroadenoma, multiple										X															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Keratoacanthoma																									X
Papilloma squamous													X												
Subcutaneous tissue, fibroma										X															
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+																					
Spinal cord				+																					
Schwannoma NOS				X																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Fibrosarcoma, metastatic, skin																									
Mediastinum, schwannoma malignant			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 6 4	0 7 6 5	0 7 7 1	0 7 7 2	0 7 7 4	0 7 8 1	0 7 8 4	0 7 9 4	0 8 0 1	0 8 0 3	0 8 0 5	0 8 1 1	0 8 1 2	0 8 1 3	0 8 1 4	0 8 1 5	0 8 2 1	0 8 2 2	0 8 2 3	0 8 2 4	0 8 3 4	0 8 3 5	0 8 4 4	Total Tissues/ Tumors
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X															1
Carcinoma															X										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign												X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal													X							X	X				7
Sarcoma stromal																									1
Hematopoietic System																									
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																						X			1
Fibroadenoma	X				X	X			X						X	X					X		X		14
Fibroadenoma, multiple																						X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign	X																								1
Keratoacanthoma																									1
Papilloma squamous																									1
Subcutaneous tissue, fibroma																									1
Subcutaneous tissue, fibrosarcoma							X								X										2
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																									1
Spinal cord																									1
Schwannoma NOS																									1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									1
Fibrosarcoma, metastatic, skin							X																		1
Mediastinum, schwannoma malignant																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 6 2	0 7 6 3	0 7 6 4	0 7 6 5	0 7 7 1	0 7 7 2	0 7 7 4	0 7 8 1	0 7 8 4	0 7 9 4	0 8 0 1	0 8 0 3	0 8 0 5	0 8 1 1	0 8 1 2	0 8 1 3	0 8 1 4	0 8 1 5	0 8 2 1	0 8 2 2	0 8 2 3	0 8 2 4	0 8 3 4	0 8 3 5	0 8 4 4	Total Tissues/ Tumors
Special Senses System																										
Eye			+																							2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm

Number of Days on Study	045	078	528	571	599	609	663	666	684	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730
Carcass ID Number	00914	00853	00972	00872	00852	00901	00951	00921	00895	00851	00854	00855	00861	00864	00865	00871	00875	00883	00884	00885	00892	00902	00912	00915	00923	00924	
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																											
Mesentery					+										+												
Liposarcoma															X												
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papilloma squamous																											
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma benign																		X									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																											
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma									X	X	X	X	X		X	X		X							X	X	
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-cell, adenoma							X				X						X								X		
C-cell, carcinoma																											
Follicular cell, carcinoma													X														
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma							X					X			X				X			X					
Carcinoma			X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Granulosa cell tumor malignant								X																			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 9 3 1	0 9 3 2	0 9 3 4	0 9 3 5	0 9 4 1	0 9 4 2	0 9 4 3	0 9 4 4	0 9 4 5	0 9 5 2	0 9 5 3	0 9 5 4	0 9 5 5	0 9 6 1	0 9 6 2	0 9 6 3	0 9 6 4	0 9 6 5	0 9 7 1	0 9 7 4	0 9 7 5	0 9 8 1	0 9 8 2	0 9 8 4	0 9 8 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma																					X					1
Mesentery																		+								3
Liposarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous								X									X									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign	X																			X		X				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma				X	X	X			X			X					X			X	X		X			19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma													X										X			6
C-cell, carcinoma																									X	1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X																									6
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Granulosa cell tumor malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	0 4 5	0 7 8	5 2 8	5 7 1	5 9 9	6 0 9	6 6 3	6 6 6	6 8 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	0 9 1 4	0 8 5 3	0 9 7 2	0 8 7 2	0 8 5 2	0 9 0 1	0 9 5 1	0 9 2 1	0 8 9 5	0 8 5 1	0 8 5 4	0 8 5 5	0 8 6 1	0 8 6 4	0 8 6 5	0 8 7 1	0 8 7 5	0 8 8 3	0 8 8 4	0 8 8 5	0 8 9 2	0 9 0 2	0 9 1 2	0 9 1 5	0 9 2 3	0 9 2 4
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																X	X		X							X
Vagina					+																					
Hematopoietic System																										
Blood	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Carcinoma, metastatic													X													
Thymoma benign														X												
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma				X		X			X			X	X	X	X	X				X	X			X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery															X											
Renal tubule, adenoma																							X			
Renal tubule, carcinoma																							X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			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 Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 9 3 1	0 9 3 2	0 9 3 4	0 9 3 5	0 9 4 1	0 9 4 2	0 9 4 3	0 9 4 4	0 9 4 5	0 9 5 2	0 9 5 3	0 9 5 4	0 9 5 5	0 9 6 1	0 9 6 2	0 9 6 3	0 9 6 4	0 9 6 5	0 9 7 1	0 9 7 4	0 9 7 5	0 9 8 1	0 9 8 2	0 9 8 4	0 9 8 5	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Polyp stromal							X																		X	6
Vagina																										1
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Deep cervical, carcinoma, metastatic, thyroid gland																									X	1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Carcinoma, metastatic																										1
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibroadenoma			X	X				X	X	X		X	X		X	X		X	X	X				X		26
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye							+																			1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liposarcoma, metastatic, mesentery																										1
Renal tubule, adenoma																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear		X	X			X	X	X			X			X	X	X	X			X				X	X	26

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 0 3 5	1 0 4 1	1 0 4 2	1 0 4 3	1 0 5 1	1 0 5 2	1 0 5 3	1 0 6 2	1 0 6 3	1 0 6 5	1 0 7 2	1 0 7 3	1 0 7 4	1 0 8 1	1 0 9 2	1 0 9 3	1 0 9 4	1 1 0 2	1 1 0 5	1 1 1 1	1 1 1 2	1 1 2 1	1 1 2 2	1 1 2 3	1 1 2 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																							X		1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesentery											+		+												2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign										X															1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X						X				X	X	X			X					X	X	X		20
Pars distalis, carcinoma																									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, C-cell, adenoma																									2
C-cell, adenoma																	X	X			X				6
Follicular cell, adenoma		X																							1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma	X																								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor benign																									1
Granulosa-theca tumor benign							X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																									1
Leiomyoma		X																							1
Polyp stromal									X								X				X	X		X	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	4 9 5	5 2 7	6 4 2	6 6 3	6 8 0	6 8 4	6 9 4	7 0 1	7 0 1	7 0 1	7 1 5	7 2 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
Carcass ID Number	1 0 1 4	1 0 2 4	1 1 1 5	1 0 4 4	1 0 8 3	0 9 9 2	1 0 8 4	1 0 5 4	1 0 9 1	1 1 2 4	1 1 0 4	1 0 6 4	0 9 9 5	1 0 0 1	1 0 0 2	1 0 1 1	1 1 1 5	1 2 2 3	1 2 2 5	1 3 3 1	1 3 3 2	1 3 4 3	1 0 3 3
Hematopoietic System																						
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle					X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Thymoma benign																						
Integumentary System																						
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X			X	X						X	X		X				
Fibroadenoma, multiple				X						X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																						
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma					X																	
Nervous System																						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland	X		X																			
Granular cell tumor benign																						
Oligodendroglioma NOS															X							
Respiratory System																						
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle					X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																						
Eye					+																	
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland																						
Urinary System																						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X				X	X	X		X		X		X			X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 0 3 5	1 0 4 1	1 0 4 2	1 0 4 3	1 0 5 1	1 0 5 2	1 0 5 3	1 0 6 2	1 0 6 3	1 0 6 5	1 0 7 2	1 0 7 3	1 0 7 4	1 0 8 1	1 0 9 2	1 0 9 3	1 0 9 4	1 1 0 2	1 1 0 5	1 1 1 1	1 1 1 2	1 1 2 1	1 1 2 2	1 1 2 3	1 1 2 5	Total Tissues/ Tumors
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mediastinal, rhabdomyosarcoma, metastatic, skeletal muscle																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Thymoma benign											X															1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma								X		X	X		X						X							11
Fibroadenoma, multiple	X				X																		X			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, pituitary gland																										2
Granular cell tumor benign											X															1
Oligodendroglioma NOS																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma														X							X					2
Mediastinum, rhabdomyosarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye			+												+				+							4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lacrimal gland	+																									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear							X	X			X		X		X				X	X			X			18

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	1/50 (2%)	0/50 (0%)	4/51 (8%)	1/48 (2%)
Adjusted rates[b]	2.7%	0.0%	9.5%	2.8%
Terminal rates[c]	1/37 (3%)	0/37 (0%)	4/42 (10%)	1/36 (3%)
First incidence (days)	729 (T)	–[e]	729 (T)	729 (T)
Life table tests[d]	P=0.552	P=0.500N	P=0.219	P=0.756
Logistic regression tests[d]	P=0.552	P=0.500N	P=0.219	P=0.756
Cochran-Armitage test[d]	P=0.547			
Fisher exact test[d]		P=0.500N	P=0.187	P=0.742
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rates	2/50 (4%)	0/50 (0%)	4/51 (8%)	1/48 (2%)
Adjusted rates	5.1%	0.0%	9.5%	2.8%
Terminal rates	1/37 (3%)	0/37 (0%)	4/42 (10%)	1/36 (3%)
First incidence (days)	694	–	729 (T)	729 (T)
Life table tests	P=0.572N	P=0.245N	P=0.389	P=0.504N
Logistic regression tests	P=0.555N	P=0.247N	P=0.349	P=0.508N
Cochran-Armitage test	P=0.581N			
Fisher exact test		P=0.247N	P=0.348	P=0.515N
Clitoral Gland: Adenoma				
Overall rates	5/49 (10%)	1/49 (2%)	6/47 (13%)	2/47 (4%)
Adjusted rates	12.7%	2.7%	14.8%	5.6%
Terminal rates	4/37 (11%)	1/37 (3%)	5/39 (13%)	2/36 (6%)
First incidence (days)	599	729 (T)	663	729 (T)
Life table tests	P=0.350N	P=0.110N	P=0.531	P=0.230N
Logistic regression tests	P=0.345N	P=0.109N	P=0.456	P=0.234N
Cochran-Armitage test	P=0.362N			
Fisher exact test		P=0.102N	P=0.470	P=0.235N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	5/49 (10%)	2/49 (4%)	7/47 (15%)	2/47 (4%)
Adjusted rates	12.7%	5.4%	16.5%	5.6%
Terminal rates	4/37 (11%)	2/37 (5%)	5/39 (13%)	2/36 (6%)
First incidence (days)	599	729 (T)	528	729 (T)
Life table tests	P=0.294N	P=0.226N	P=0.409	P=0.230N
Logistic regression tests	P=0.300N	P=0.233N	P=0.353	P=0.234N
Cochran-Armitage test	P=0.304N			
Fisher exact test		P=0.218N	P=0.350	P=0.235N
Mammary Gland: Fibroadenoma				
Overall rates	19/50 (38%)	16/50 (32%)	26/51 (51%)	16/48 (33%)
Adjusted rates	45.9%	40.9%	57.7%	38.5%
Terminal rates	15/37 (41%)	14/37 (38%)	23/42 (55%)	11/36 (31%)
First incidence (days)	624	667	571	663
Life table tests	P=0.390N	P=0.352N	P=0.246	P=0.358N
Logistic regression tests	P=0.349N	P=0.421N	P=0.109	P=0.374N
Cochran-Armitage test	P=0.427N			
Fisher exact test		P=0.338N	P=0.133	P=0.393N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rates	19/50 (38%)	17/50 (34%)	26/51 (51%)	16/48 (33%)
Adjusted rates	45.9%	43.5%	57.7%	38.5%
Terminal rates	15/37 (41%)	15/37 (41%)	23/42 (55%)	11/36 (31%)
First incidence (days)	624	667	571	663
Life table tests	P=0.355N	P=0.430N	P=0.246	P=0.358N
Logistic regression tests	P=0.312N	P=0.510N	P=0.109	P=0.374N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.418N	P=0.133	P=0.393N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	23/50 (46%)	17/50 (34%)	19/51 (37%)	20/47 (43%)
Adjusted rates	53.1%	42.0%	44.2%	48.3%
Terminal rates	17/37 (46%)	14/37 (38%)	18/42 (43%)	14/35 (40%)
First incidence (days)	585	548	684	663
Life table tests	P=0.513	P=0.188N	P=0.154N	P=0.409N
Logistic regression tests	P=0.531	P=0.179N	P=0.267N	P=0.431N
Cochran-Armitage test	P=0.474			
Fisher exact test		P=0.154N	P=0.245N	P=0.446N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	23/50 (46%)	18/50 (36%)	19/51 (37%)	22/47 (47%)
Adjusted rates	53.1%	44.5%	44.2%	50.4%
Terminal rates	17/37 (46%)	15/37 (41%)	18/42 (43%)	14/35 (40%)
First incidence (days)	585	548	684	495
Life table tests	P=0.371	P=0.245N	P=0.154N	P=0.552N
Logistic regression tests	P=0.360	P=0.243N	P=0.267N	P=0.543
Cochran-Armitage test	P=0.323			
Fisher exact test		P=0.208N	P=0.245N	P=0.549
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	0/50 (0%)	3/50 (6%)	0/51 (0%)	0/48 (0%)
Adjusted rates	0.0%	7.7%	0.0%	0.0%
Terminal rates	0/37 (0%)	2/37 (5%)	0/42 (0%)	0/36 (0%)
First incidence (days)	–	667	–	–
Life table tests	P=0.255N	P=0.120	–	–
Logistic regression tests	P=0.259N	P=0.113	–	–
Cochran-Armitage test	P=0.262N			
Fisher exact test		P=0.121	–	–
Thyroid Gland (C-cell): Adenoma				
Overall rates	8/50 (16%)	7/50 (14%)	6/50 (12%)	8/48 (17%)
Adjusted rates	19.8%	18.9%	13.9%	21.3%
Terminal rates	6/37 (16%)	7/37 (19%)	5/42 (12%)	7/36 (19%)
First incidence (days)	599	729 (T)	663	684
Life table tests	P=0.486	P=0.511N	P=0.314N	P=0.589
Logistic regression tests	P=0.506	P=0.545N	P=0.390N	P=0.578
Cochran-Armitage test	P=0.466			
Fisher exact test		P=0.500N	P=0.387N	P=0.572

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	9/50 (18%)	9/50 (18%)	7/50 (14%)	8/48 (17%)
Adjusted rates	22.4%	24.3%	16.2%	21.3%
Terminal rates	7/37 (19%)	9/37 (24%)	6/42 (14%)	7/36 (19%)
First incidence (days)	599	729 (T)	663	684
Life table tests	P=0.472N	P=0.593	P=0.311N	P=0.519N
Logistic regression tests	P=0.444N	P=0.551	P=0.397N	P=0.530N
Cochran-Armitage test	P=0.491N			
Fisher exact test		P=0.602N	P=0.393N	P=0.537N
Uterus: Stromal Polyp				
Overall rates	13/50 (26%)	7/50 (14%)	6/51 (12%)	7/48 (15%)
Adjusted rates	34.1%	17.5%	14.3%	18.9%
Terminal rates	12/37 (32%)	5/37 (14%)	6/42 (14%)	6/36 (17%)
First incidence (days)	694	451	729 (T)	715
Life table tests	P=0.207N	P=0.109N	P=0.033N	P=0.115N
Logistic regression tests	P=0.185N	P=0.128N	P=0.043N	P=0.099N
Cochran-Armitage test	P=0.218N			
Fisher exact test		P=0.105N	P=0.057N	P=0.125N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	13/50 (26%)	8/50 (16%)	6/51 (12%)	7/48 (15%)
Adjusted rates	34.1%	19.1%	14.3%	18.9%
Terminal rates	12/37 (32%)	5/37 (14%)	6/42 (14%)	6/36 (17%)
First incidence (days)	694	396	729 (T)	715
Life table tests	P=0.177N	P=0.169N	P=0.033N	P=0.115N
Logistic regression tests	P=0.173N	P=0.158N	P=0.043N	P=0.099N
Cochran-Armitage test	P=0.186N			
Fisher exact test		P=0.163N	P=0.057N	P=0.125N
All Organs: Mononuclear Cell Leukemia				
Overall rates	19/50 (38%)	21/50 (42%)	26/51 (51%)	18/48 (38%)
Adjusted rates	42.5%	51.2%	54.1%	43.6%
Terminal rates	12/37 (32%)	17/37 (46%)	20/42 (48%)	13/36 (36%)
First incidence (days)	599	609	528	527
Life table tests	P=0.400N	P=0.398	P=0.244	P=0.527N
Logistic regression tests	P=0.398N	P=0.344	P=0.123	P=0.571N
Cochran-Armitage test	P=0.434N			
Fisher exact test		P=0.419	P=0.133	P=0.563N
All Organs: Benign Neoplasms				
Overall rates	40/50 (80%)	36/50 (72%)	43/51 (84%)	36/48 (75%)
Adjusted rates	88.8%	79.9%	93.5%	80.0%
Terminal rates	32/37 (86%)	28/37 (76%)	39/42 (93%)	27/36 (75%)
First incidence (days)	585	451	571	663
Life table tests	P=0.391N	P=0.319N	P=0.451N	P=0.327N
Logistic regression tests	P=0.311N	P=0.372N	P=0.246	P=0.315N
Cochran-Armitage test	P=0.455N			
Fisher exact test		P=0.241N	P=0.380	P=0.363N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	24/50 (48%)	26/50 (52%)	30/51 (59%)	22/48 (46%)
Adjusted rates	51.7%	60.2%	61.2%	49.5%
Terminal rates	15/37 (41%)	20/37 (54%)	23/42 (55%)	14/36 (39%)
First incidence (days)	585	396	528	495
Life table tests	P=0.338N	P=0.397	P=0.333	P=0.460N
Logistic regression tests	P=0.359N	P=0.412	P=0.174	P=0.550N
Cochran-Armitage test	P=0.364N			
Fisher exact test		P=0.421	P=0.187	P=0.495N
All Organs: Benign or Malignant Neoplasms				
Overall rates	45/50 (90%)	47/50 (94%)	49/51 (96%)	42/48 (88%)
Adjusted rates	91.8%	95.9%	100.0%	87.5%
Terminal rates	33/37 (89%)	35/37 (95%)	42/42 (100%)	30/36 (83%)
First incidence (days)	585	396	528	495
Life table tests	P=0.285N	P=0.369	P=0.516N	P=0.411N
Logistic regression tests	P=0.189N	P=0.312	P=0.041	P=0.475N
Cochran-Armitage test	P=0.248N			
Fisher exact test		P=0.357	P=0.210	P=0.471N

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths			1	
Moribund	6	11	6	11
Natural deaths	7	2	2	1
Survivors				
Terminal sacrifice	37	37	42	36
Missexed				2
Animals examined microscopically	70	61	62	68
9-Month Interim Evaluation				
Alimentary System				
Pancreas	(10)			(10)
Acinus, atrophy				2 (20%)
Cardiovascular System				
Heart	(9)			(10)
Degeneration, chronic	2 (22%)			2 (20%)
Endocrine System				
Pituitary gland	(10)			(10)
Pars distalis, congestion				1 (10%)
Pars distalis, hyperplasia	1 (10%)			1 (10%)
General Body System				
None				
Genital System				
Clitoral gland	(10)			(6)
Duct, cyst				1 (17%)
Oviduct	(1)			
Dilatation	1 (100%)			
Inflammation, acute	1 (100%)			
Hematopoietic System				
None				
Integumentary System				
None				

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
9-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)		(2)	(10)
Nephropathy, chronic	1 (10%)		2 (100%)	2 (20%)
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(2)	(1)	(10)
Basophilic focus	8 (80%)	1 (50%)	1 (100%)	10 (100%)
Clear cell focus	1 (10%)		1 (100%)	2 (20%)
Hepatodiaphragmatic nodule	1 (10%)	2 (100%)	1 (100%)	3 (30%)
Inflammation, chronic	5 (50%)		1 (100%)	7 (70%)
Mesentery		(1)	(2)	
Inflammation, chronic active			1 (50%)	
Necrosis		1 (100%)	1 (50%)	
Pancreas	(10)	(1)		(10)
Acinus, atrophy	1 (10%)	1 (100%)		2 (20%)
Salivary glands	(10)	(1)		(10)
Atrophy				1 (10%)
Cardiovascular System				
Heart	(10)	(1)		(10)
Cardiomyopathy, chronic				1 (10%)
Endocrine System				
Pituitary gland	(10)	(1)		(10)
Pars distalis, angiectasis	1 (10%)			
Pars distalis, cyst	7 (70%)	1 (100%)		3 (30%)
Pars distalis, hyperplasia				1 (10%)
Thyroid gland	(10)	(1)		(10)
C-cell, hyperplasia				2 (20%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
15-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Clitoral gland	(10)	(2)		(10)
Inflammation, chronic active	4 (40%)	2 (100%)		3 (30%)
Ovary	(10)	(3)		(10)
Cyst	1 (10%)	2 (67%)		
Uterus	(10)	(1)	(2)	(10)
Dilatation				1 (10%)
Inflammation, chronic active	1 (10%)			
Endometrium, hyperplasia, cystic, glandular	1 (10%)			1 (10%)
Hematopoietic System				
None				
Integumentary System				
Mammary gland	(8)	(1)		(10)
Hyperplasia, cystic	7 (88%)	1 (100%)		10 (100%)
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(1)		(10)
Inflammation, chronic active		1 (100%)		
Nose	(10)	(1)		(10)
Fungus				1 (10%)
Inflammation, chronic active				1 (10%)
Nasolacrimal duct, inflammation, suppurative	2 (20%)	1 (100%)		1 (10%)
Special Senses System				
Eye	(1)			
Lens, cataract	1 (100%)			
Retina, atrophy	1 (100%)			
Harderian gland	(10)	(1)		(10)
Inflammation, chronic active				1 (10%)
Urinary System				
Kidney	(10)	(9)	(8)	(10)
Nephropathy, chronic	9 (90%)	9 (100%)	8 (100%)	10 (100%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study				
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(48)
Parasite metazoan	1 (2%)			2 (4%)
Intestine large, rectum	(50)	(50)	(50)	(48)
Inflammation, chronic active				1 (2%)
Parasite metazoan	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Intestine small, jejunum	(50)	(50)	(50)	(48)
Inflammation, chronic active		2 (4%)		
Liver	(50)	(50)	(51)	(48)
Bacterium				1 (2%)
Basophilic focus	37 (74%)	41 (82%)	35 (69%)	36 (75%)
Clear cell focus	4 (8%)	3 (6%)	3 (6%)	5 (10%)
Degeneration, cystic		2 (4%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	4 (8%)
Hepatodiaphragmatic nodule	6 (12%)	7 (14%)	5 (10%)	5 (10%)
Hyperplasia	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic	29 (58%)	35 (70%)	30 (59%)	36 (75%)
Leukocytosis	1 (2%)			1 (2%)
Necrosis, coagulative	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Thrombus	1 (2%)			
Vacuolization cytoplasmic	16 (32%)	15 (30%)	18 (35%)	17 (35%)
Bile duct, cyst	1 (2%)	1 (2%)		
Bile duct, hyperplasia	36 (72%)	31 (62%)	35 (69%)	33 (69%)
Mesentery	(3)	(3)	(3)	(2)
Inflammation, necrotizing	2 (67%)	3 (100%)	1 (33%)	1 (50%)
Pancreas	(50)	(49)	(50)	(48)
Infiltration cellular, lipocyte	34 (68%)	31 (63%)	36 (72%)	27 (56%)
Inflammation, chronic active		1 (2%)		
Acinus, amyloid deposition	1 (2%)			
Acinus, atrophy	9 (18%)	15 (31%)	13 (26%)	10 (21%)
Perivascular, inflammation, chronic active	1 (2%)			1 (2%)
Salivary glands	(50)	(50)	(50)	(48)
Acinus, hyperplasia	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(48)
Acanthosis	4 (8%)	5 (10%)	4 (8%)	7 (15%)
Hyperkeratosis	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic active	3 (6%)	3 (6%)	1 (2%)	3 (6%)
Perforation				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(48)
Erosion	1 (2%)	1 (2%)		
Inflammation, chronic active	4 (8%)	4 (8%)		1 (2%)
Mineralization		1 (2%)		
Tooth	(50)	(50)	(51)	(48)
Inflammation, chronic active		3 (6%)	2 (4%)	3 (6%)
Cardiovascular System				
Heart	(50)	(50)	(51)	(48)
Cardiomyopathy, chronic	38 (76%)	32 (64%)	34 (67%)	37 (77%)
Atrium, thrombus	1 (2%)	1 (2%)	2 (4%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(51)	(48)
Degeneration, fatty	27 (54%)	23 (46%)	28 (55%)	27 (56%)
Hematocyst	1 (2%)			
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	25 (50%)	23 (46%)	24 (47%)	20 (42%)
Hypertrophy	5 (10%)	2 (4%)	3 (6%)	1 (2%)
Adrenal gland, medulla	(50)	(50)	(51)	(48)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	12 (24%)	11 (22%)	6 (12%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(48)
Hyperplasia		1 (2%)		1 (2%)
Vacuolization cytoplasmic		1 (2%)		
Parathyroid gland	(46)	(46)	(46)	(46)
Hyperplasia	1 (2%)			
Pituitary gland	(50)	(50)	(51)	(47)
Craniopharyngeal duct, cyst	1 (2%)		2 (4%)	2 (4%)
Pars distalis, cyst	30 (60%)	28 (56%)	23 (45%)	25 (53%)
Pars distalis, hyperplasia	22 (44%)	24 (48%)	24 (47%)	18 (38%)
Pars intermedia, cyst	1 (2%)		1 (2%)	
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(48)
C-cell, hyperplasia	17 (34%)	12 (24%)	9 (18%)	17 (35%)
Follicular cell, cyst				1 (2%)
Follicular cell, hyperplasia		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(49)	(49)	(47)	(47)
Hyperplasia	5 (10%)	4 (8%)	10 (21%)	6 (13%)
Inflammation, chronic active	17 (35%)	13 (27%)	12 (26%)	20 (43%)
Duct, ectasia	1 (2%)	1 (2%)		1 (2%)
Ovary	(50)	(50)	(51)	(48)
Atrophy		3 (6%)	1 (2%)	1 (2%)
Cyst	5 (10%)	5 (10%)	4 (8%)	2 (4%)
Uterus	(50)	(50)	(51)	(48)
Dilatation		1 (2%)	2 (4%)	
Hemorrhage			1 (2%)	
Hyperplasia, cystic, glandular	3 (6%)	4 (8%)	8 (16%)	5 (10%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Intussusception		1 (2%)		
Endometrium, hyperplasia	1 (2%)			
Vagina	(1)		(1)	
Inflammation, suppurative	1 (100%)		1 (100%)	
Hematopoietic System				
Blood	(41)	(48)	(48)	(48)
Polycythemia				1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Bone marrow	(50)	(50)	(51)	(48)
Femoral, hyperplasia, erythrocyte				1 (2%)
Femoral, myelofibrosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lymph node	(50)	(50)	(51)	(48)
Deep cervical, inflammation, chronic active		1 (2%)		
Inguinal, cyst		1 (2%)		
Lumbar, cyst		1 (2%)		
Mediastinal, inflammation, chronic active	1 (2%)			
Lymph node, mandibular	(50)	(50)	(50)	(47)
Cyst	4 (8%)		2 (4%)	3 (6%)
Hyperplasia, plasma cell			1 (2%)	
Spleen	(50)	(50)	(51)	(48)
Fibrosis			2 (4%)	
Hematopoietic cell proliferation	2 (4%)	3 (6%)	1 (2%)	4 (8%)
Lymphoid follicle, hyperplasia	1 (2%)			1 (2%)
Thymus	(46)	(48)	(47)	(45)
Cyst	2 (4%)	2 (4%)		1 (2%)
Ectopic parathyroid gland	1 (2%)			
Integumentary System				
Mammary gland	(48)	(49)	(51)	(46)
Hyperplasia, cystic	46 (96%)	48 (98%)	49 (96%)	46 (100%)
Skin	(50)	(50)	(51)	(47)
Cyst epithelial inclusion	1 (2%)			
Inflammation, chronic active		1 (2%)		2 (4%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(51)	(48)
Compression	4 (8%)	7 (14%)	1 (2%)	3 (6%)
Hydrocephalus	3 (6%)	6 (12%)	1 (2%)	5 (10%)
Necrosis				1 (2%)
Respiratory System				
Lung	(50)	(50)	(51)	(48)
Bacterium				1 (2%)
Infiltration cellular, histiocyte	27 (54%)	35 (70%)	32 (63%)	29 (60%)
Inflammation, chronic active	8 (16%)	7 (14%)	8 (16%)	9 (19%)
Leukocytosis				1 (2%)
Metaplasia, osseous	4 (8%)			
Necrosis, coagulative				1 (2%)
Alveolar epithelium, hyperplasia	1 (2%)	4 (8%)	6 (12%)	4 (8%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(50)	(51)	(48)
Fungus	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Inflammation, chronic active	3 (6%)	2 (4%)	6 (12%)	4 (8%)
Nasolacrimal duct, inflammation, suppurative	17 (34%)	14 (28%)	16 (31%)	20 (42%)
Special Senses System				
Eye	(3)	(2)	(1)	(4)
Cornea, inflammation, chronic active		1 (50%)		
Lens, cataract	2 (67%)	2 (100%)	1 (100%)	4 (100%)
Retina, atrophy	2 (67%)	2 (100%)	1 (100%)	3 (75%)
Urinary System				
Kidney	(50)	(50)	(51)	(48)
Bacterium				1 (2%)
Hydronephrosis				1 (2%)
Inflammation, chronic active				1 (2%)
Necrosis, coagulative	1 (2%)			
Nephropathy, chronic	48 (96%)	50 (100%)	49 (96%)	48 (100%)
Thrombus	1 (2%)			
Renal tubule, hyperplasia		2 (4%)		
Renal tubule, hyperplasia, oncocytic	1 (2%)			
Urinary bladder	(49)	(50)	(51)	(48)
Inflammation, hemorrhagic				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 FEED STUDY OF MANGANESE (II) SULFATE MONOHYDRATE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	10	10	10	9
15-Month interim evaluation[c]	10	10	9	10
Early deaths				
Accidental deaths				1
Moribund	2	3	2	1
Natural deaths	2	3	3	3
Survivors				
Died last week of study	1	1		
Terminal sacrifice	45	43	46	46
Animals examined microscopically	70	61	61	70
9-Month Interim Evaluation				
Alimentary System				
Intestine small, duodenum	(10)	(1)		(9)
Polyp adenomatous		1 (100%)		
Liver	(10)			(9)
Hepatocellular adenoma	1 (10%)			
Respiratory System				
Lung	(10)			(9)
Alveolar/bronchiolar adenoma	1 (10%)			
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Hepatocellular adenoma				1 (10%)
Endocrine System				
Thyroid gland	(10)	(2)	(1)	(10)
Follicular cell, adenoma				1 (10%)
Special Senses System				
Harderian gland	(1)			
Adenoma	1 (100%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study				
Alimentary System				
Intestine large, cecum	(48)	(49)	(49)	(50)
Adenocarcinoma			1 (2%)	
Intestine small	(50)	(49)	(50)	(50)
Intestine small, duodenum	(49)	(49)	(50)	(50)
Polyp adenomatous	1 (2%)		1 (2%)	
Intestine small, jejunum	(49)	(49)	(50)	(50)
Adenocarcinoma		2 (4%)		
Liver	(50)	(49)	(51)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	1 (2%)
Hepatocellular carcinoma	5 (10%)	10 (20%)	6 (12%)	4 (8%)
Hepatocellular carcinoma, multiple	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Hepatocellular adenoma	14 (28%)	12 (24%)	5 (10%)	11 (22%)
Hepatocellular adenoma, multiple	16 (32%)	17 (35%)	14 (27%)	9 (18%)
Sarcoma	1 (2%)			
Mesentery	(2)		(1)	
Hepatocellular carcinoma, metastatic, liver			1 (100%)	
Pancreas	(50)	(49)	(50)	(50)
Stomach, forestomach	(50)	(49)	(51)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		
Cardiovascular System				
Heart	(50)	(49)	(51)	(51)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal gland	(50)	(49)	(51)	(49)
Spindle cell, adenoma	10 (20%)	5 (10%)	7 (14%)	14 (29%)
Adrenal gland, cortex	(49)	(49)	(51)	(49)
Adenoma		3 (6%)	1 (2%)	1 (2%)
Adrenal gland, medulla	(49)	(47)	(48)	(49)
Pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(50)	(49)	(50)	(50)
Adenoma			2 (4%)	
Thyroid gland	(50)	(49)	(51)	(50)
Follicular cell, adenoma				3 (6%)
General Body System				
None				
Genital System				
Epididymis	(50)	(49)	(51)	(50)
Fibrosarcoma			1 (2%)	
Hemangiosarcoma		1 (2%)		
Prostate	(50)	(49)	(51)	(50)
Hemangiosarcoma		1 (2%)		
Testes	(50)	(49)	(51)	(50)
Interstitial cell, carcinoma			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(49)	(51)	(50)
Femoral, hemangiosarcoma		1 (2%)		
Lymph node	(48)	(49)	(51)	(50)
Bronchial, hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Mediastinal, hepatocellular carcinoma, metastatic, liver		1 (2%)		
Thoracic, hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Lymph node, mandibular	(46)	(43)	(50)	(50)
Lymph node, mesenteric	(43)	(46)	(45)	(48)
Spleen	(50)	(49)	(50)	(50)
Fibrosarcoma		2 (4%)		
Hemangiosarcoma		1 (2%)	2 (4%)	
Thymus	(39)	(42)	(47)	(42)
Integumentary System				
Skin	(50)	(49)	(51)	(50)
Squamous cell papilloma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(49)	(51)	(51)
Hemangiosarcoma		1 (2%)		
Nervous System				
None				
Respiratory System				
Lung	(50)	(49)	(51)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	9 (18%)	5 (10%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	5 (10%)	4 (8%)	4 (8%)	4 (8%)
Carcinoma, metastatic, testes			1 (2%)	
Hepatocellular carcinoma, metastatic, liver		4 (8%)	3 (6%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Special Senses System				
Ear		(1)		(2)
Pinna, fibroma		1 (100%)		1 (50%)
Harderian gland	(5)	(4)	(3)	(5)
Adenocarcinoma	1 (20%)			4 (80%)
Adenoma	4 (80%)	2 (50%)	2 (67%)	1 (20%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(49)	(51)	(50)
Carcinoma, metastatic, testes			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Systemic Lesions				
Multiple organs[d]	(50)	(49)	(51)	(51)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)	
Lymphoma malignant mixed	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Lymphoma malignant undifferentiated cell		1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[e]				
9-Month interim evaluation	2	1		
15-Month interim evaluation	1			2
2-Year study	46	44	40	39
Total primary neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	1			2
2-Year study	75	80	62	66
Total animals with benign neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	1			2
2-Year study	38	39	31	32
Total benign neoplasms				
9-Month interim evaluation	2	1		
15-Month interim evaluation	1			2
2-Year study	53	51	39	49
Total animals with malignant neoplasms				
2-Year study	20	24	21	15
Total malignant neoplasms				
2-Year study	22	29	23	17
Total animals with metastatic neoplasms				
2-Year study	1	4	4	2
Total metastatic neoplasms				
2-Year study	5	5	6	2

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were observed in the cardiovascular, endocrine, general body, genital, hematopoietic, integumentary, musculoskeletal, nervous, special senses, and urinary systems in any animal at the 9-month interim evaluation.
[c] No neoplasms were seen in the cardiovascular, general body, genital, hematopoietic, integumentary, musculoskeletal, nervous, respiratory, and urinary systems in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm

Number of Days on Study	4666	6877	7099	7255	7299	7299	7299	7299	7299	7299	7299	7299	7299	7300	7300	7300	7300	7300	7300	7300	7300	7300	7311	7311	7311
Carcass ID Number	00381	00481	00211	00511	00021	00031	00051	00061	00071	00091	00101	00111	00141	00151	00161	00171	00181	00191	00201	00221	00241	00251	00261	00271	00281
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	I	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous												X													
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma	X			X	X																				
Hepatocellular carcinoma, multiple								X						X											
Hepatocellular adenoma				X			X			X								X		X	X				
Hepatocellular adenoma, multiple					X			X							X	X			X				X	X	X
Sarcoma	X																								
Mesentery									+									+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver	X																								
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																			X	X					
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	0 3 0 1	0 3 1 1	0 3 2 1	0 3 6 1	0 3 7 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 4 1	0 4 5 1	0 4 6 1	0 4 7 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 9 1	0 6 0 1	0 6 1 1	0 6 2 1	0 6 3 1	0 6 4 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 9 1	0 7 0 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	49
Polyp adenomatous																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																						1
Hepatocellular carcinoma		X												X													5
Hepatocellular carcinoma, multiple											X					X											4
Hepatocellular adenoma			X	X								X	X	X				X	X			X					14
Hepatocellular adenoma, multiple		X				X	X	X							X	X									X	X	16
Sarcoma																											1
Mesentery																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma		X	X	X		X					X						X							X		X	10
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	M	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
None																											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	4666	6871	7099	7225	7229	7299	7299	7299	7299	7299	7299	7299	7299	7300	7300	7300	7300	7300	7300	7300	7300	7300	7301	7311	7331
Carcass ID Number	00381	00481	00211	00511	00021	00031	00051	00061	00071	00091	00101	00111	00141	00151	00161	00171	00181	00191	00201	00221	00241	00251	00261	00271	00281
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+		+			+			+	+	+	+	+	+	+	+		+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, hepatocholangiocarcinoma, metastatic, liver	X																								
Thoracic, hepatocholangiocarcinoma, metastatic, liver	X																								
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+																							
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X	X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma						X		X	X	X															
Hepatocholangiocarcinoma, metastatic, liver	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland															+	+	+								
Adenocarcinoma															X										
Adenoma																X	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	0 3 0 1	0 3 1 1	0 3 2 1	0 3 6 1	0 3 7 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 5 1	0 4 6 1	0 4 7 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 9 1	0 6 0 1	0 6 1 1	0 6 2 1	0 6 3 1	0 6 4 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 9 1	0 7 0 1	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+				+		+	+		+	+			+		+				+	31
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	48
Bronchial, hepatocholangiocarcinoma, metastatic, liver																										1
Thoracic, hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+		+	M	+		+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	M	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	M	39
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X								X										X					X		6
Alveolar/bronchiolar adenoma, multiple				X																						1
Alveolar/bronchiolar carcinoma																						X				5
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland		+				+																				5
Adenocarcinoma																										1
Adenoma		X				X																				4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	4 6 6	6 8 7	7 0 9	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 3 8 1	0 4 8 1	0 2 1 1	0 5 1 1	0 0 2 1	0 0 3 1	0 0 5 1	0 0 6 1	0 0 7 1	0 0 9 1	0 1 0 1	0 1 1 1	0 1 4 1	0 1 5 1	0 1 6 1	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 2 1	0 2 4 1	0 2 5 1	0 2 6 1	0 2 7 1	0 2 8 1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic												X													
Lymphoma malignant mixed			X								X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	0 3 0 1	0 3 1 1	0 3 2 1	0 3 6 1	0 3 7 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 5 1	0 4 6 1	0 4 7 1	0 5 4 1	0 5 5 1	0 5 6 1	0 5 9 1	0 6 0 1	0 6 1 1	0 6 2 1	0 6 3 1	0 6 4 1	0 6 5 1	0 6 6 1	0 6 7 1	0 6 9 1	0 7 0 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed			X																	X						4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 0 3 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 7 1	1 0 8 1	1 1 1 1	1 1 4 1	1 1 8 1	1 1 5 1	1 1 6 1	1 1 7 1	1 1 8 1	1 2 0 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 6 1	1 2 7 1	1 2 8 1	1 2 9 1	1 3 0 1	1 3 1 1	1 3 2 1	1 3 3 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																									2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma							X		X			X					X					X			10
Hepatocellular carcinoma, multiple																									2
Hepatocellular adenoma					X		X		X			X		X									X		12
Hepatocellular adenoma, multiple		X									X		X				X	X			X				X	17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spindle cell, adenoma				X						X			X												5
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																						X			1
Preputial gland	+	+	+	+			+			+	+							+		+	+		+		26
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X																							1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	6 1 7	6 4 7	6 7 9	7 0 1	7 0 8	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	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1
Carcass ID Number	1 3 5 1	1 2 5 1	1 1 3 1	1 3 6 1	1 1 9 1	0 7 1 1	0 7 3 1	0 7 4 1	0 7 6 1	0 7 7 1	0 7 8 1	0 8 1 1	0 8 2 1	0 8 5 1	0 8 7 1	0 8 9 1	0 9 1 1	0 9 2 1	0 9 3 1	0 9 6 1	0 9 8 1	0 9 9 1	1 0 0 1	1 0 1 1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma										X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, hepatocellular carcinoma, metastatic, liver				X																				
Lymph node, mandibular	+	+	+		+	+	+	+	+	+	M	+	+	+	+	M	+	+		+	+	+	+	+
Lymph node, mesenteric	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								
Hemangiosarcoma																								
Thymus	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X						X				X	X	X					X	X			
Alveolar/bronchiolar adenoma, multiple		X																						
Alveolar/bronchiolar carcinoma													X					X						
Hepatocellular carcinoma, metastatic, liver				X	X	X												X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Pinna, fibroma																								
Harderian gland	+																							+
Adenoma	X																							
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed																			X			X		
Lymphoma malignant undifferentiated cell type																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 0 3 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 7 1	1 0 8 1	1 1 1 1	1 1 4 1	1 3 8 1	1 1 5 1	1 1 6 1	1 1 7 1	1 1 8 1	1 2 0 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 6 1	1 2 7 1	1 2 8 1	1 2 9 1	1 3 0 1	1 3 1 1	1 3 2 1	1 3 3 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma								X											X							2
Hemangiosarcoma																				X						1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	A	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma				X													X									9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma									X		X															4
Hepatocellular carcinoma, metastatic, liver																										4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear	+																									1
Pinna, fibroma	X																									1
Harderian gland								+													+					4
Adenoma								X																		2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic															X											1
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type																									X	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	1 7 6 1	1 7 8 1	1 8 0 1	1 8 1 1	1 8 3 1	1 8 4 1	1 8 5 1	1 8 6 1	1 8 7 1	1 8 9 1	1 9 0 1	1 9 2 1	1 9 3 1	1 9 4 1	1 9 5 1	1 9 7 1	1 9 9 1	2 0 1 1	2 0 2 1	2 0 3 1	2 0 4 1	2 0 5 1	2 0 7 1	2 0 9 1	2 1 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																										1
Hepatocellular carcinoma	X							X						X												6
Hepatocellular carcinoma, multiple							X								X											2
Hepatocellular adenoma																			X		X					5
Hepatocellular adenoma, multiple	X													X	X			X						X	X	14
Mesentery															+											1
Hepatocellular carcinoma, metastatic, liver															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spindle cell, adenoma																				X	X			X		7
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adenoma																				X						1
Adrenal gland, medulla	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	73131	73111	73111	73111	73111	73111	73111	73122	73222	73222	73222	73222	73222	73222	73222	73222	73233	73333	73333	73333	73333	73333	73333	73333	73333	73333	
Carcass ID Number	17761	17781	18001	18081	18083	18084	18085	18086	18087	18089	19001	19021	19031	19041	19051	19071	19091	20011	20021	20031	20041	20051	20071	20091	20101		Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Fibrosarcoma																						X					1
Preputial gland		+		+	+						+	+	+				+	+	+	+			+	+			20
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Interstitial cell, carcinoma																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Lymph node, mandibular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma	X	X																									2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+		47
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Squamous cell papilloma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Alveolar/bronchiolar adenoma			X							X					X	X	X										5
Alveolar/bronchiolar carcinoma									X													X					4
Carcinoma, metastatic, testes																											1
Hepatocellular carcinoma, metastatic, liver	X														X												3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Special Senses System																											
Eye																											1
Harderian gland		+																									3
Adenoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Carcinoma, metastatic, testes																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51
Lymphoma malignant lymphocytic											X																2
Lymphoma malignant mixed									X							X											3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	2 4 4 1	2 4 8 1	2 4 9 1	2 5 0 1	2 5 1 1	2 5 3 1	2 5 4 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1	2 6 1 1	2 6 2 1	2 6 5 1	2 6 6 1	2 6 9 1	2 7 0 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 7 6 1	2 7 7 1	2 7 8 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Hemangiosarcoma																		X								1
Hepatocellular carcinoma	X			X																					X	4
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X		X	X										X		X				X						11
Hepatocellular adenoma, multiple						X												X			X	X				9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spindle cell, adenoma			X		X			X		X	X		X	X	X	X										14
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma														X												3
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+						+	+	+		+	+		+	+	+			+	+		+	+	30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	5 0

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	2 4 4 1	2 4 8 1	2 4 9 1	2 5 0 1	2 5 1 1	2 5 3 1	2 5 4 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1	2 6 1 1	2 6 2 1	2 6 5 1	2 6 6 1	2 6 9 1	2 7 0 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 7 6 1	2 7 7 1	2 7 8 1	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	42
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X	X					X	X					8
Alveolar/bronchiolar adenoma, multiple																							X			1
Alveolar/bronchiolar carcinoma																						X			X	4
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear													+													2
Pinna, fibroma																										1
Harderian gland									+									+		+						5
Adenocarcinoma									X									X								4
Adenoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant mixed																										2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	0/49 (0%)	3/49 (6%)	1/51 (2%)	1/49 (2%)
Adjusted rates[b]	0.0%	6.8%	2.2%	2.2%
Terminal rates[c]	0/45 (0%)	3/44 (7%)	1/46 (2%)	1/45 (2%)
First incidence (days)	–[e]	729 (T)	729 (T)	729 (T)
Life table tests[d]	P=0.578N	P=0.117	P=0.504	P=0.500
Logistic regression tests[d]	P=0.578N	P=0.117	P=0.504	P=0.500
Cochran-Armitage test[d]	P=0.582N			
Fisher exact test[d]		P=0.121	P=0.510	P=0.500
Adrenal Gland: Spindle Cell Adenoma				
Overall rates	10/50 (20%)	5/49 (10%)	7/51 (14%)	14/49 (29%)
Adjusted rates	21.7%	11.4%	15.2%	31.1%
Terminal rates	10/46 (22%)	5/44 (11%)	7/46 (15%)	14/45 (31%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.042	P=0.151N	P=0.297N	P=0.220
Logistic regression tests	P=0.042	P=0.151N	P=0.297N	P=0.220
Cochran-Armitage test	P=0.040			
Fisher exact test		P=0.140N	P=0.282N	P=0.224
Harderian Gland: Adenoma				
Overall rates	4/50 (8%)	2/49 (4%)	2/51 (4%)	1/51 (2%)
Adjusted rates	8.7%	4.3%	4.2%	2.2%
Terminal rates	4/46 (9%)	1/44 (2%)	1/46 (2%)	1/46 (2%)
First incidence (days)	729 (T)	617	592	729 (T)
Life table tests	P=0.183N	P=0.356N	P=0.339N	P=0.180N
Logistic regression tests	P=0.157N	P=0.363N	P=0.311N	P=0.180N
Cochran-Armitage test	P=0.177N			
Fisher exact test		P=0.349N	P=0.329N	P=0.175N
Harderian Gland: Carcinoma				
Overall rates	1/50 (2%)	0/49 (0%)	0/51 (0%)	4/51 (8%)
Adjusted rates	2.2%	0.0%	0.0%	8.4%
Terminal rates	1/46 (2%)	0/44 (0%)	0/46 (0%)	3/46 (7%)
First incidence (days)	729 (T)	–	–	634
Life table tests	P=0.016	P=0.509N	P=0.500N	P=0.182
Logistic regression tests	P=0.016	P=0.509N	P=0.500N	P=0.188
Cochran-Armitage test	P=0.016			
Fisher exact test		P=0.505N	P=0.495N	P=0.187
Harderian Gland: Adenoma or Carcinoma				
Overall rates	5/50 (10%)	2/49 (4%)	2/51 (4%)	5/51 (10%)
Adjusted rates	10.9%	4.3%	4.2%	10.6%
Terminal rates	5/46 (11%)	1/44 (2%)	1/46 (2%)	4/46 (9%)
First incidence (days)	729 (T)	617	592	634
Life table tests	P=0.368	P=0.235N	P=0.219N	P=0.629
Logistic regression tests	P=0.398	P=0.234N	P=0.198N	P=0.628N
Cochran-Armitage test	P=0.373			
Fisher exact test		P=0.226N	P=0.210N	P=0.617N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Liver: Hepatocellular Adenoma				
Overall rates	30/50 (60%)	29/49 (59%)	19/51 (37%)	20/50 (40%)
Adjusted rates	63.8%	64.4%	40.4%	42.5%
Terminal rates	29/46 (63%)	28/44 (64%)	18/46 (39%)	19/46 (41%)
First incidence (days)	725	708	702	645
Life table tests	P=0.017N	P=0.555	P=0.023N	P=0.037N
Logistic regression tests	P=0.025N	P=0.525	P=0.024N	P=0.045N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.548N	P=0.018N	P=0.036N
Liver: Hepatocellular Carcinoma				
Overall rates	9/50 (18%)	12/49 (24%)	8/51 (16%)	6/50 (12%)
Adjusted rates	18.7%	26.1%	16.6%	13.0%
Terminal rates	7/46 (15%)	10/44 (23%)	6/46 (13%)	6/46 (13%)
First incidence (days)	466	701	417	729 (T)
Life table tests	P=0.131N	P=0.280	P=0.500N	P=0.294N
Logistic regression tests	P=0.121N	P=0.282	P=0.420N	P=0.272N
Cochran-Armitage test	P=0.127N			
Fisher exact test		P=0.294	P=0.482N	P=0.288N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	34/50 (68%)	31/49 (63%)	24/51 (47%)	22/50 (44%)
Adjusted rates	70.8%	67.4%	49.0%	46.8%
Terminal rates	32/46 (70%)	29/44 (66%)	21/46 (46%)	21/46 (46%)
First incidence (days)	466	701	417	645
Life table tests	P=0.010N	P=0.455N	P=0.044N	P=0.015N
Logistic regression tests	P=0.010N	P=0.385N	P=0.029N	P=0.014N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.388N	P=0.027N	P=0.013N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	7/50 (14%)	10/49 (20%)	5/51 (10%)	9/50 (18%)
Adjusted rates	15.2%	21.6%	10.9%	20.0%
Terminal rates	7/46 (15%)	8/44 (18%)	5/46 (11%)	9/45 (20%)
First incidence (days)	729 (T)	647	729 (T)	729 (T)
Life table tests	P=0.448	P=0.268	P=0.379N	P=0.374
Logistic regression tests	P=0.430	P=0.280	P=0.379N	P=0.374
Cochran-Armitage test	P=0.462			
Fisher exact test		P=0.282	P=0.366N	P=0.393
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	5/50 (10%)	4/49 (8%)	4/51 (8%)	4/50 (8%)
Adjusted rates	10.9%	9.1%	8.7%	8.9%
Terminal rates	5/46 (11%)	4/44 (9%)	4/46 (9%)	4/45 (9%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.497N	P=0.528N	P=0.500N	P=0.514N
Logistic regression tests	P=0.497N	P=0.528N	P=0.500N	P=0.514N
Cochran-Armitage test	P=0.488N			
Fisher exact test		P=0.513N	P=0.487N	P=0.500N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	12/50 (24%)	13/49 (27%)	9/51 (18%)	12/50 (24%)
Adjusted rates	26.1%	28.1%	19.6%	26.7%
Terminal rates	12/46 (26%)	11/44 (25%)	9/46 (20%)	12/45 (27%)
First incidence (days)	729 (T)	647	729 (T)	729 (T)
Life table tests	P=0.534N	P=0.451	P=0.311N	P=0.569
Logistic regression tests	P=0.551	P=0.477	P=0.311N	P=0.569
Cochran-Armitage test	P=0.517N			
Fisher exact test		P=0.477	P=0.294N	P=0.592N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	0/50 (0%)	0/49 (0%)	0/51 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	0.0%	6.5%
Terminal rates	0/46 (0%)	0/44 (0%)	0/46 (0%)	3/46 (7%)
First incidence (days)	–	–	–	729 (T)
Life table tests	P=0.015	–	–	P=0.121
Logistic regression tests	P=0.015	–	–	P=0.121
Cochran-Armitage test	P=0.015			
Fisher exact test		–	–	P=0.121
All Organs: Hemangiosarcoma				
Overall rates	1/50 (2%)	5/49 (10%)	3/51 (6%)	1/51 (2%)
Adjusted rates	2.2%	11.0%	6.5%	2.2%
Terminal rates	1/46 (2%)	4/44 (9%)	3/46 (7%)	1/46 (2%)
First incidence (days)	729 (T)	647	729 (T)	729 (T)
Life table tests	P=0.263N	P=0.097	P=0.306	P=0.761
Logistic regression tests	P=0.262N	P=0.093	P=0.306	P=0.761
Cochran-Armitage test	P=0.255N			
Fisher exact test		P=0.098	P=0.316	P=0.748N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	5/50 (10%)	4/49 (8%)	5/51 (10%)	2/51 (4%)
Adjusted rates	10.6%	9.1%	10.9%	4.2%
Terminal rates	4/46 (9%)	4/44 (9%)	5/46 (11%)	1/46 (2%)
First incidence (days)	709	729 (T)	729 (T)	645
Life table tests	P=0.183N	P=0.530N	P=0.628	P=0.225N
Logistic regression tests	P=0.185N	P=0.520N	P=0.625	P=0.207N
Cochran-Armitage test	P=0.175N			
Fisher exact test		P=0.513N	P=0.617N	P=0.210N
All Organs: Benign Neoplasms				
Overall rates	39/50 (78%)	39/49 (80%)	31/51 (61%)	33/51 (65%)
Adjusted rates	83.0%	81.2%	63.3%	70.2%
Terminal rates	38/46 (83%)	35/44 (80%)	28/46 (61%)	32/46 (70%)
First incidence (days)	725	617	592	645
Life table tests	P=0.080N	P=0.434	P=0.071N	P=0.126N
Logistic regression tests	P=0.097N	P=0.530	P=0.068N	P=0.188N
Cochran-Armitage test	P=0.059N			
Fisher exact test		P=0.521	P=0.048N	P=0.104N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	20/50 (40%)	24/49 (49%)	21/51 (41%)	15/51 (29%)
Adjusted rates	40.8%	50.0%	43.7%	31.2%
Terminal rates	17/46 (37%)	20/44 (45%)	19/46 (41%)	13/46 (28%)
First incidence (days)	466	647	417	634
Life table tests	P=0.076N	P=0.229	P=0.499	P=0.217N
Logistic regression tests	P=0.059N	P=0.248	P=0.543	P=0.184N
Cochran-Armitage test	P=0.057N			
Fisher exact test		P=0.243	P=0.533	P=0.182N
All Organs: Benign or Malignant Neoplasms				
Overall rates	47/50 (94%)	44/49 (90%)	40/51 (78%)	39/51 (76%)
Adjusted rates	95.9%	89.8%	80.0%	79.6%
Terminal rates	44/46 (96%)	39/44 (89%)	36/46 (78%)	36/46 (78%)
First incidence (days)	466	617	417	634
Life table tests	P=0.038N	P=0.502N	P=0.076N	P=0.044N
Logistic regression tests	P=0.019N	P=0.345N	P=0.032N	P=0.023N
Cochran-Armitage test	P=0.011N			
Fisher exact test		P=0.346N	P=0.022N	P=0.013N

(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, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, 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 control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	**Carcinoma**	**Adenoma or Carcinoma**
Historical Incidence at Battelle Columbus Laboratories			
2,4-Dichlorophenol	2/50	0/50	2/50
5,5-Diphenylhydantoin	0/49	0/49	0/49
Dowicide EC-7 Pentachlorophenol	0/35	0/35	0/35
Ethylene thiourea	0/50	1/50	1/50
Polybrominated biphenyls (Firemaster FF-1®)	1/50	0/50	1/50
Manganese (II) sulfate monohydrate	0/50	0/50	0/50
Technical Grade Pentachlorophenol	1/31	0/31	1/31
Triamterene	0/50	0/50	0/50
Triamterene	1/50	0/50	1/50
Overall Historical Incidence			
Total	19/1,105 (1.7%)	5/1,105 (0.5%)	24/1,105 (2.2%)
Standard deviation	1.7%	0.8%	2.0%
Range	0%-4%	0%-2%	0%-6%

[a] Data as of 17 December 1991

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	9
15-Month interim evaluation	10	10	9	10
Early deaths				
Accidental deaths				1
Moribund	2	3	2	1
Natural deaths	2	3	3	3
Survivors				
Died last week of study	1	1		
Terminal sacrifice	45	43	46	46
Animals examined microscopically	70	61	61	70
9-Month Interim Evaluation				
Alimentary System				
Liver	(10)			(9)
Mineralization, focal				1 (11%)
Centrilobular, vacuolization cytoplasmic	7 (70%)			3 (33%)
Cardiovascular System				
None				
Endocrine System				
Thyroid gland	(10)			(9)
Follicle, dilatation				6 (67%)
General Body System				
None				
Genital System				
Preputial gland	(1)			(1)
Duct, dilatation	1 (100%)			1 (100%)
Testes	(10)		(1)	(9)
Interstitial cell, hyperplasia			1 (100%)	
Seminiferous tubule, atrophy			1 (100%)	
Hematopoietic System				
None				
Integumentary System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
9-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Basophilic focus			3 (33%)	
Clear cell focus		1 (10%)	1 (11%)	1 (10%)
Mixed cell focus				1 (10%)
Vacuolization cytoplasmic	7 (70%)	5 (50%)	5 (56%)	6 (60%)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, cortex	(10)			(10)
Hypertrophy	1 (10%)			
Islets, pancreatic	(10)			(10)
Hyperplasia	3 (30%)			2 (20%)
Thyroid gland	(10)	(2)	(1)	(10)
Follicle, cyst		2 (100%)	1 (100%)	2 (20%)
Follicle, dilatation				9 (90%)
General Body System				
None				
Genital System				
Preputial gland	(1)			
Inflammation, chronic active	1 (100%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mesenteric	(7)			(9)
Infiltration cellular, plasma cell	1 (14%)			
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Renal tubule, regeneration	10 (100%)			6 (60%)
2-Year Study				
Alimentary System				
Gallbladder	(42)	(47)	(50)	(50)
Artery, inflammation, chronic active	1 (2%)			
Intestine small, jejunum	(49)	(49)	(50)	(50)
Diverticulum				1 (2%)
Liver	(50)	(49)	(51)	(50)
Basophilic focus	1 (2%)		1 (2%)	
Clear cell focus	2 (4%)	10 (20%)	5 (10%)	
Eosinophilic focus	1 (2%)	6 (12%)	3 (6%)	1 (2%)
Hepatodiaphragmatic nodule			1 (2%)	
Hypertrophy	1 (2%)			
Infarct	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic active		1 (2%)		1 (2%)
Necrosis	2 (4%)			
Vacuolization cytoplasmic	20 (40%)	16 (33%)	18 (35%)	18 (36%)
Bile duct, hyperplasia	1 (2%)			
Mesentery	(2)		(1)	
Fat, inflammation, chronic active	2 (100%)			
Pancreas	(50)	(49)	(50)	(50)
Acinus, atrophy	2 (4%)	2 (4%)		3 (6%)
Duct, cyst	2 (4%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(49)	(51)	(50)
Erosion, focal				2 (4%)
Hyperplasia, focal, squamous	2 (4%)	1 (2%)	5 (10%)	14 (28%)
Inflammation, chronic active				5 (10%)
Ulcer				6 (12%)
Stomach, glandular	(49)	(49)	(51)	(49)
Dysplasia			1 (2%)	
Hyperplasia		1 (2%)		
Tooth			(1)	
Incisor, abscess			1 (100%)	
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(50)	(49)	(51)	(49)
Spindle cell, accessory adrenal cortical nodule			1 (2%)	
Spindle cell, vacuolization cytoplasmic	1 (2%)			
Adrenal gland, cortex	(49)	(49)	(51)	(49)
Accessory adrenal cortical nodule	1 (2%)			
Atrophy	1 (2%)			
Hyperplasia	3 (6%)	3 (6%)	5 (10%)	1 (2%)
Hypertrophy	26 (53%)	37 (76%)	35 (69%)	26 (53%)
Vacuolization cytoplasmic		1 (2%)		
Adrenal gland, medulla	(49)	(47)	(48)	(49)
Cyst				1 (2%)
Hyperplasia	1 (2%)			
Islets, pancreatic	(50)	(49)	(50)	(50)
Hyperplasia		5 (10%)	2 (4%)	1 (2%)
Parathyroid gland	(46)	(48)	(46)	(48)
Cyst		2 (4%)		
Pituitary gland	(46)	(44)	(49)	(46)
Pars distalis, cyst	2 (4%)	1 (2%)		2 (4%)
Pars distalis, hyperplasia				1 (2%)
Pars distalis, karyomegaly				1 (2%)
Pars intermedia, hyperplasia			1 (2%)	
Pars intermedia, hyperplasia, focal			1 (2%)	
Rathke's cleft, cyst			1 (2%)	
Thyroid gland	(50)	(49)	(51)	(50)
Inflammation, chronic active			2 (4%)	1 (2%)
Follicle, cyst	1 (2%)	5 (10%)	6 (12%)	3 (6%)
Follicle, dilatation	2 (4%)	2 (4%)	5 (10%)	23 (46%)
Follicular cell, hyperplasia, focal	5 (10%)	2 (4%)	8 (16%)	27 (54%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Genital System				
Preputial gland	(31)	(26)	(20)	(30)
Inflammation, chronic active	4 (13%)		2 (10%)	1 (3%)
Duct, dilatation	28 (90%)	25 (96%)	18 (90%)	29 (97%)
Seminal vesicle	(50)	(49)	(51)	(51)
Inflammation, chronic active		2 (4%)		
Testes	(50)	(49)	(51)	(50)
Granuloma sperm			1 (2%)	
Seminiferous tubule, atrophy	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic System				
Lymph node, mandibular	(46)	(43)	(50)	(50)
Depletion lymphoid	1 (2%)			
Lymph node, mesenteric	(43)	(46)	(45)	(48)
Hematopoietic cell proliferation	1 (2%)	7 (15%)	2 (4%)	
Spleen	(50)	(49)	(50)	(50)
Depletion lymphoid	1 (2%)			
Hematopoietic cell proliferation		4 (8%)	1 (2%)	2 (4%)
Necrosis	1 (2%)			
Thymus	(39)	(42)	(47)	(42)
Depletion lymphoid	4 (10%)	5 (12%)	4 (9%)	5 (12%)
Infiltration cellular, polymorphonuclear		1 (2%)		
Integumentary System				
Skin	(50)	(49)	(51)	(50)
Alopecia	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Ulcer	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Subcutaneous tissue, inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Musculoskeletal System				
None				
Nervous System				
Peripheral nerve	(1)			
Sciatic, demyelination	1 (100%)			
Spinal cord	(1)			
Demyelination	1 (100%)			
Respiratory System				
Lung	(50)	(49)	(51)	(50)
Inflammation, chronic active	1 (2%)			
Alveolar epithelium, hyperplasia			4 (8%)	1 (2%)
Nose	(50)	(49)	(51)	(50)
Mucosa, inflammation, acute	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Special Senses System				
Eye			(1)	
Cornea, inflammation, chronic active			1 (100%)	
Harderian gland	(5)	(4)	(3)	(5)
Hyperplasia		1 (25%)	1 (33%)	
Acinus, dilatation		1 (25%)		
Urinary System				
Kidney	(50)	(49)	(51)	(50)
Hydronephrosis	1 (2%)	1 (2%)		
Inflammation, chronic active				1 (2%)
Nephropathy	47 (94%)	48 (98%)	46 (90%)	47 (94%)
Cortex, cyst		3 (6%)		
Urinary bladder	(48)	(49)	(51)	(49)
Lumen, hemorrhage				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 FEED STUDY OF MANGANESE (II) SULFATE MONOHYDRATE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation[b]	10	10	10	10
15-Month interim evaluation[c]	9	10	9	9
Early deaths				
Accidental deaths	1			
Moribund	6	4	6	4
Natural deaths	2		6	5
Survivors				
Terminal sacrifice	42	46	38	42
Missing			1	
Animals examined microscopically	70	61	62	70
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(10)	(9)	(9)
Hepatocellular adenoma			2 (22%)	
2-Year Study				
Alimentary System				
Intestine large, cecum	(51)	(50)	(49)	(51)
Intestine small, duodenum	(51)	(49)	(50)	(50)
Adenocarcinoma				1 (2%)
Intestine small, jejunum	(51)	(50)	(50)	(51)
Liver	(51)	(50)	(50)	(51)
Hemangiosarcoma	1 (2%)			
Hepatocellular carcinoma	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Hepatocellular adenoma	11 (22%)	11 (22%)	6 (12%)	9 (18%)
Hepatocellular adenoma, multiple	1 (2%)	3 (6%)		3 (6%)
Osteosarcoma, metastatic, bone			1 (2%)	1 (2%)
Mesentery	(8)	(3)	(1)	
Fibrosarcoma, metastatic	1 (13%)			
Pancreas	(51)	(50)	(50)	(51)
Fibrosarcoma, metastatic, skin	1 (2%)			
Salivary glands	(51)	(50)	(50)	(50)
Neurofibrosarcoma, metastatic, skin			1 (2%)	
Stomach, forestomach	(51)	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)			
Stomach, glandular	(51)	(50)	(50)	(49)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(51)	(50)	(50)	(51)
Spindle cell, adenoma		2 (4%)	3 (6%)	
Adrenal gland, cortex	(51)	(50)	(48)	(51)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal gland, medulla	(51)	(50)	(48)	(51)
Pheochromocytoma benign	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(48)	(46)	(50)	(49)
Pars distalis, adenoma	2 (4%)	3 (7%)	6 (12%)	5 (10%)
Pars intermedia, adenoma			2 (4%)	1 (2%)
Thyroid gland	(50)	(50)	(49)	(51)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma	2 (4%)	1 (2%)		5 (10%)
General Body System				
None				
Genital System				
Ovary	(51)	(50)	(50)	(51)
Adenoma		2 (4%)		
Cystadenoma	1 (2%)		1 (2%)	2 (4%)
Cystadenoma, papillary	1 (2%)			
Granulosa cell tumor benign		1 (2%)		
Teratoma malignant				1 (2%)
Bilateral, adenocarcinoma, metastatic		1 (2%)		
Uterus	(51)	(50)	(50)	(51)
Adenocarcinoma		2 (4%)		
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)			1 (2%)
Polyp stromal	1 (2%)	1 (2%)		2 (4%)
Sarcoma stromal		1 (2%)		
Cervix, leiomyoma	1 (2%)			
Cervix, osteosarcoma, metastatic, bone			1 (2%)	
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(51)
Femoral, hemangiosarcoma		3 (6%)		
Lymph node	(51)	(50)	(49)	(50)
Lymph node, mandibular	(49)	(50)	(47)	(46)
Lymph node, mesenteric	(48)	(48)	(44)	(45)
Hemangiosarcoma				1 (2%)
Spleen	(51)	(50)	(50)	(51)
Fibrosarcoma	1 (2%)			
Hemangiosarcoma		2 (4%)		2 (4%)
Thymus	(49)	(49)	(47)	(46)
Thymoma benign	1 (2%)			
Integumentary System				
Skin	(51)	(50)	(50)	(51)
Subcutaneous tissue, fibrosarcoma	2 (4%)			
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, neurofibrosarcoma	1 (2%)		3 (6%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(51)	(50)	(50)	(51)
Femur, osteosarcoma				2 (4%)
Pelvis, osteosarcoma			1 (2%)	
Nervous System				
None				
Respiratory System				
Lung	(51)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma	4 (8%)		3 (6%)	
Fibrosarcoma, metastatic, skin	1 (2%)			
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	1 (2%)
Teratoma malignant, metastatic, ovary				1 (2%)
Special Senses System				
Harderian gland	(6)	(3)	(2)	
Adenocarcinoma	1 (17%)			
Adenoma	2 (33%)	3 (100%)	2 (100%)	
Urinary System				
Kidney	(51)	(50)	(50)	(51)
Urinary bladder	(51)	(50)	(49)	(50)
Osteosarcoma, metastatic, bone			1 (2%)	
Systemic Lesions				
Multiple organs[d]	(51)	(50)	(50)	(51)
Lymphoma malignant histiocytic	4 (8%)	3 (6%)	5 (10%)	2 (4%)
Lymphoma malignant lymphocytic	4 (8%)	4 (8%)	4 (8%)	2 (4%)
Lymphoma malignant mixed	7 (14%)	10 (20%)	12 (24%)	9 (18%)
Neoplasm Summary				
Total animals with primary neoplasms[e]				
15-Month interim evaluation			2	
2-Year study	37	37	37	36
Total primary neoplasms				
15-Month interim evaluation			2	
2-Year study	57	59	52	56
Total animals with benign neoplasms				
15-Month interim evaluation			2	
2-Year study	21	24	16	25

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Neoplasm Summary (continued)				
Total benign neoplasms				
15-Month interim evaluation			2	
2-Year study	28	32	23	32
Total animals with malignant neoplasms				
2-Year study	23	23	26	21
Total malignant neoplasms				
2-Year study	29	27	29	24
Total animals with metastatic neoplasms				
2-Year study	1	1	2	3
Total metastatic neoplasms				
2-Year study	3	1	5	4

[a] Number of animals examined microscopically at site and number of animals with lesion
[b] No neoplasms were observed at any site in any aninal at the 9-month interim evaluation.
[c] No neoplasms were observed in the cardiovascular, endocrine, general body, genital, hematopoietic, integumentary, musculoskeletal, nervous, respiratory, special senses, and urinary systems in any animal at the 15-month interim evaluation.
[d] Number of animals with any tissue examined microscopically
[e] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	3 1 4 1	3 1 5 1	3 1 9 1	3 2 2 1	3 2 4 1	3 2 6 1	3 2 8 1	3 3 1 1	3 3 2 1	3 3 5 1	3 3 7 1	3 3 9 1	4 0 1 1	4 4 1 1	4 4 2 1	4 4 3 1	4 4 4 1	4 4 5 1	4 4 7 1	4 4 8 1	4 4 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma																X										1
Hepatocellular carcinoma											X															3
Hepatocellular adenoma		X		X					X				X													11
Hepatocellular adenoma, multiple																X										1
Mesentery						+										+										8
Fibrosarcoma, metastatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Fibrosarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma											X															2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
Tissue NOS																			+							1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	2 7 7	3 2 3	3 9 7	5 3 7	6 0 7	6 2 0	6 9 6	7 0 8	7 2 0	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	7 3 0	7 3 0	7 3 1
Carcass ID Number	3 0 7 1	3 0 3 1	3 0 5 1	3 3 4 1	3 2 7 1	2 9 1 1	3 3 1 1	2 9 0 1	3 2 3 1	2 8 1 1	2 8 2 1	2 8 3 1	2 8 7 1	2 8 8 1	2 8 9 1	2 9 3 1	2 9 4 1	2 9 5 1	2 9 7 1	2 9 8 1	2 9 9 1	3 0 2 1	3 0 4 1	3 0 6 1	3 0 8 1	3 0 9 1
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Cystadenoma, papillary																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																							X		
Polyp stromal																									
Cervix, leiomyoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thymoma benign																X									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma					X				X																
Subcutaneous tissue, neurofibrosarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+	+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma						X							X									X			
Fibrosarcoma, metastatic, skin									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	3 1 4 1	3 1 5 1	3 1 9 1	3 2 2 1	3 2 4 1	3 2 6 1	3 2 8 1	3 3 1 1	3 3 2 1	3 3 5 1	3 3 7 1	3 3 9 1	4 0 1	4 1 1	4 2 1	4 3 1	4 4 1	4 4 5 1	4 4 7 1	4 4 8 1	4 4 9 1	Total Tissues/ Tumors	
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Cystadenoma				X																						1	
Cystadenoma, papillary																	X									1	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Hemangioma																			X							1	
Hemangiosarcoma																										1	
Polyp stromal																X										1	
Cervix, leiomyoma													X													1	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymph node, mandibular	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	48	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Fibrosarcoma																										1	
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymoma benign																										1	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	43	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Subcutaneous tissue, fibrosarcoma																										2	
Subcutaneous tissue, neurofibrosarcoma																										1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Skeletal muscle																										1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Spinal cord																										2	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Alveolar/bronchiolar adenoma															X											2	
Alveolar/bronchiolar carcinoma							X																			4	
Fibrosarcoma, metastatic, skin																										1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		51

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 0 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	3 1 4 1	3 1 5 1	3 1 9 1	3 2 2 1	3 2 4 1	3 2 6 1	3 2 8 1	3 3 1 1	3 3 2 1	3 3 5 1	3 3 7 1	3 3 9 1	4 4 0 1	4 4 1 1	4 4 2 1	4 4 3 1	4 4 4 1	4 4 5 1	4 4 7 1	4 4 8 1	4 4 9 1	Total Tissues/ Tumors	
Special Senses System																												
Ear		+																									1	
Harderian gland							+							+					+	+		+		+			6	
Adenocarcinoma																			X								1	
Adenoma																				X		X					2	
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Lymphoma malignant histiocytic												X		X													4	
Lymphoma malignant lymphocytic	X																						X				4	
Lymphoma malignant mixed							X	X							X	X			X						X			7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm

Number of Days on Study	679	701	712	720	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731
Carcass ID Number	36521	40211	39311	37411	55211	55311	55511	56111	55711	55811	55911	56011	56111	56311	56611	56711	56811	57011	57111	57311	57511	57711	57811	58011	58211	58311
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																										
Hepatocellular adenoma		X			X	X			X			X													X	X
Hepatocellular adenoma, multiple																					X			X		
Mesentery																+								+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma					X																					
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+
Pars distalis, adenoma			X			X								X												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										
General Body System																										
Tissue NOS															+											
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																			
Granulosa cell tumor benign				X																						
Bilateral, adenocarcinoma, metastatic	X																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X																									
Polyp stromal																										
Sarcoma stromal																	X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 8 1	3 8 9 1	3 9 2 1	3 9 5 1	3 9 6 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 3 1	4 0 4 1	4 0 6 1	4 0 7 1	4 0 8 1	4 0 9 1	4 1 0 1	4 1 1 1	4 1 3 1	4 1 4 1	4 1 5 1	4 1 6 1	4 1 8 1	4 2 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							1
Hepatocellular adenoma				X											X			X							X	11
Hepatocellular adenoma, multiple													X													3
Mesentery																						+				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma																								X		2
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								1
General Body System																										
Tissue NOS																										1
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							2
Granulosa cell tumor benign																										1
Bilateral, adenocarcinoma, metastatic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															2
Polyp stromal				X																						1
Sarcoma stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	679	701	712	720	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	731	731	731
Carcass ID Number	36521	40211	39311	37411	55211	55311	55511	55611	55711	55811	55911	56011	56111	56311	56711	56811	57011	57111	57311	57511	57711	57811	58011	58211	58311
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma											X											X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																	X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland						+								+											
Adenoma						X								X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																							X		
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed						X											X			X				X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 1,500 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	3 8 4 1	3 8 6 1	3 8 8 1	3 8 9 1	3 9 2 1	3 9 5 1	3 9 6 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 3 1	4 0 4 1	4 0 6 1	4 0 7 1	4 0 8 1	4 0 9 1	4 1 0 1	4 1 1 1	4 1 3 1	4 1 4 1	4 1 5 1	4 1 6 1	4 1 8 1	4 2 0 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma														X												3
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							2
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X		X																					4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																			+							3
Adenoma																			X							3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic									X								X									3
Lymphoma malignant lymphocytic						X							X		X											4
Lymphoma malignant mixed	X		X							X										X			X		X	10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm

Number of Days on Study	1 0 7	4 0 9	4 8 8	5 5 4	6 0 7	6 1 0	6 9 3	6 9 6	7 0 2	7 0 4	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 7 5 1	4 3 9 1	4 9 0 1	4 7 7 1	4 5 4 1	4 7 1 1	4 2 9 1	4 3 7 1	4 4 1 1	4 7 9 1	4 3 1 1	4 4 0 1	4 2 2 1	4 2 3 1	4 2 4 1	4 2 6 1	4 2 7 1	4 3 0 1	4 3 2 1	4 3 8 1	4 4 2 1	4 4 3 1	4 4 5 1	4 4 6 1	4 4 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X																
Hepatocellular adenoma								X																	X
Osteosarcoma, metastatic, bone							X																		
Mesentery																						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, metastatic, skin					X																				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																					X				
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cervix, osteosarcoma, metastatic, bone							X																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	4 4 8 1	4 4 9 1	4 5 3 1	4 5 6 1	4 5 7 1	4 5 8 1	4 5 9 1	4 6 0 1	4 6 1 1	4 6 2 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 6 9 1	4 7 0 1	4 7 2 1	4 7 4 1	4 7 8 1	4 8 0 1	4 8 1 1	4 8 2 1	4 8 4 1	4 8 5 1	4 8 8 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									1
Hepatocellular adenoma					X				X									X				X			6
Osteosarcoma, metastatic, bone																									1
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibrosarcoma, metastatic, skin																									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spindle cell, adenoma									X												X				3
Adrenal gland, cortex	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	48
Adrenal gland, medulla	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X		X	X									X	X				X			6
Pars intermedia, adenoma																X						X			2
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cervix, osteosarcoma, metastatic, bone																									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	1 0 7	4 0 9	4 8 8	5 5 4	6 0 7	6 1 0	6 9 3	6 9 6	7 0 2	7 0 4	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	4 7 5 1	4 3 9 1	4 9 0 1	4 7 7 1	4 5 4 1	4 7 1 1	4 2 9 1	4 3 7 1	4 4 1 1	4 7 9 1	4 3 1 1	4 4 0 1	4 2 2 1	4 2 3 1	4 2 4 1	4 2 6 1	4 2 7 1	4 3 0 1	4 3 2 1	4 3 8 1	4 4 2 1	4 4 3 1	4 4 5 1	4 4 6 1	4 4 7 1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, neurofibrosarcoma		X	X		X																			
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, osteosarcoma							X																	
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X				X		
Alveolar/bronchiolar carcinoma																								
Osteosarcoma, metastatic, bone							X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone							X																	
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X		X			X	X									X					
Lymphoma malignant lymphocytic																				X				X
Lymphoma malignant mixed					X						X						X					X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 5,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	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	
Carcass ID Number	4 4 8 1	4 4 9 1	4 5 3 1	4 5 6 1	4 5 7 1	4 5 8 1	4 5 9 1	4 6 0 1	4 6 1 1	4 6 2 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 6 9 1	4 7 0 1	4 7 2 1	4 7 4 1	4 7 8 1	4 8 0 1	4 8 1 1	4 8 2 1	4 8 4 1	4 8 5 1	4 8 8 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	M	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		+	M		M	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	M	M	+	+	+	+		+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	39
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, neurofibrosarcoma																										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							3
Alveolar/bronchiolar carcinoma		X		X																			X			3
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+		+																							2
Adenoma	X		X																							2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, bone																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										5
Lymphoma malignant lymphocytic			X			X																				4
Lymphoma malignant mixed		X						X					X	X			X		X			X		X		12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm

Number of Days on Study	447	473	488	631	676	689	696	709	726	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730
Carcass ID Number	49601	56001	50801	52201	54501	55001	55401	55201	55801	49101	49201	49301	49401	49501	49701	49801	49901	50001	50201	50401	50901	51101	51201	51601	51801	51901
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X														
Intestine small, ileum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									X	
Hepatocellular adenoma									X		X								X							
Hepatocellular adenoma, multiple																										
Osteosarcoma, metastatic, bone							X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma																										
Pars intermedia, adenoma		X																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma																						X				
Follicular cell, adenoma																							X			
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																										X
Teratoma malignant	X																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Polyp stromal														X												

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 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	
Carcass ID Number	5 2 0 1	5 2 1 1	5 2 3 1	5 2 6 1	5 2 7 1	5 2 9 1	5 3 0 1	5 3 3 1	5 3 5 1	5 3 6 1	5 3 7 1	5 3 8 1	5 4 0 1	5 4 1 1	5 4 2 1	5 4 3 1	5 4 4 1	5 4 7 1	5 4 9 1	5 5 1 1	5 5 3 1	5 5 5 1	5 5 6 1	5 5 7 1	5 5 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma																									X	2
Hepatocellular adenoma				X					X						X			X						X	X	9
Hepatocellular adenoma, multiple			X																X				X			3
Osteosarcoma, metastatic, bone																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign														X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X		X						X		X											5
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
C-cell, carcinoma																										1
Follicular cell, adenoma					X								X						X		X					5
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Cystadenoma			X																							2
Teratoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma											X															1
Polyp stromal																			X							2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate: 15,000 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 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	
Carcass ID Number	5 2 0 1	5 2 1 1	5 2 3 1	5 2 6 1	5 2 7 1	5 2 9 1	5 3 0 1	5 3 3 1	5 3 5 1	5 3 6 1	5 3 7 1	5 3 8 1	5 4 0 1	5 4 1 1	5 4 2 1	5 4 3 1	5 4 4 1	5 4 7 1	5 4 9 1	5 5 1 1	5 5 3 1	5 5 5 1	5 5 6 1	5 5 7 1	5 5 9 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+		+	46
Lymph node, mesenteric	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangiosarcoma											X															1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma															X											2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	M	+	+	37
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Femur, osteosarcoma													X													2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma						X		X														X				4
Hepatocellular carcinoma, metastatic, liver																									X	1
Osteosarcoma, metastatic, bone																										1
Teratoma malignant, metastatic, ovary																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye									+																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																			X							2
Lymphoma malignant mixed		X		X		X			X					X									X			9

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Adrenal Gland: Spindle Cell Adenoma				
Overall rates[a]	0/51 (0%)	2/50 (4%)	3/50 (6%)	0/51 (0%)
Adjusted rates[b]	0.0%	4.3%	7.9%	0.0%
Terminal rates[c]	0/42 (0%)	2/46 (4%)	3/38 (8%)	0/42 (0%)
First incidence (days)	–[e]	729 (T)	729 (T)	–
Life table tests[d]	P=0.395N	P=0.259	P=0.104	–
Logistic regression tests[d]	P=0.395N	P=0.259	P=0.104	–
Cochran-Armitage test[d]	P=0.379N			
Fisher exact test[d]		P=0.243	P=0.118	–
Bone Marrow: Hemangiosarcoma				
Overall rates	0/51 (0%)	3/50 (6%)	0/50 (0%)	0/51 (0%)
Adjusted rates	0.0%	6.5%	0.0%	0.0%
Terminal rates	0/42 (0%)	3/46 (7%)	0/38 (0%)	0/42 (0%)
First incidence (days)	–	729 (T)	–	–
Life table tests	P=0.264N	P=0.138	–	–
Logistic regression tests	P=0.264N	P=0.138	–	–
Cochran-Armitage test	P=0.254N			
Fisher exact test		P=0.118	–	–
Harderian Gland: Adenoma				
Overall rates	2/51 (4%)	3/50 (6%)	2/50 (4%)	0/51 (0%)
Adjusted rates	4.8%	6.5%	5.3%	0.0%
Terminal rates	2/42 (5%)	3/46 (7%)	2/38 (5%)	0/42 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–
Life table tests	P=0.125N	P=0.541	P=0.658	P=0.238N
Logistic regression tests	P=0.125N	P=0.541	P=0.658	P=0.238N
Cochran-Armitage test	P=0.115N			
Fisher exact test		P=0.491	P=0.684	P=0.248N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	3/51 (6%)	3/50 (6%)	2/50 (4%)	0/51 (0%)
Adjusted rates	7.1%	6.5%	5.3%	0.0%
Terminal rates	3/42 (7%)	3/46 (7%)	2/38 (5%)	0/42 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	–
Life table tests	P=0.080N	P=0.620N	P=0.546N	P=0.121N
Logistic regression tests	P=0.080N	P=0.620N	P=0.546N	P=0.121N
Cochran-Armitage test	P=0.073N			
Fisher exact test		P=0.652	P=0.509N	P=0.121N
Liver: Hepatocellular Adenoma				
Overall rates	12/51 (24%)	14/50 (28%)	6/50 (12%)	12/51 (24%)
Adjusted rates	27.8%	29.7%	15.2%	27.9%
Terminal rates	11/42 (26%)	13/46 (28%)	5/38 (13%)	11/42 (26%)
First incidence (days)	607	701	696	726
Life table tests	P=0.535N	P=0.516	P=0.140N	P=0.590N
Logistic regression tests	P=0.502N	P=0.475	P=0.106N	P=0.566N
Cochran-Armitage test	P=0.483N			
Fisher exact test		P=0.387	P=0.105N	P=0.592N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Liver: Hepatocellular Carcinoma				
Overall rates	3/51 (6%)	1/50 (2%)	1/50 (2%)	2/51 (4%)
Adjusted rates	6.8%	2.2%	2.4%	4.8%
Terminal rates	2/42 (5%)	1/46 (2%)	0/38 (0%)	2/42 (5%)
First incidence (days)	607	729 (T)	702	729 (T)
Life table tests	P=0.612N	P=0.278N	P=0.332N	P=0.498N
Logistic regression tests	P=0.597N	P=0.333N	P=0.312N	P=0.498N
Cochran-Armitage test	P=0.597N			
Fisher exact test		P=0.316N	P=0.316N	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	13/51 (25%)	15/50 (30%)	7/50 (14%)	13/51 (25%)
Adjusted rates	30.1%	31.9%	17.2%	30.2%
Terminal rates	12/42 (29%)	14/46 (30%)	5/38 (13%)	12/42 (29%)
First incidence (days)	607	701	696	726
Life table tests	P=0.538N	P=0.523	P=0.157N	P=0.588N
Logistic regression tests	P=0.502N	P=0.485	P=0.116N	P=0.562N
Cochran-Armitage test	P=0.483N			
Fisher exact test		P=0.388	P=0.115N	P=0.590N
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/51 (4%)	4/50 (8%)	3/50 (6%)	4/51 (8%)
Adjusted rates	4.8%	8.5%	7.9%	9.2%
Terminal rates	2/42 (5%)	3/46 (7%)	3/38 (8%)	3/42 (7%)
First incidence (days)	729 (T)	720	729 (T)	689
Life table tests	P=0.364	P=0.381	P=0.454	P=0.340
Logistic regression tests	P=0.377	P=0.379	P=0.454	P=0.348
Cochran-Armitage test	P=0.387			
Fisher exact test		P=0.329	P=0.491	P=0.339
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	4/51 (8%)	0/50 (0%)	3/50 (6%)	0/51 (0%)
Adjusted rates	9.2%	0.0%	7.9%	0.0%
Terminal rates	3/42 (7%)	0/46 (0%)	3/38 (8%)	0/42 (0%)
First incidence (days)	620	–	729 (T)	–
Life table tests	P=0.132N	P=0.054N	P=0.550N	P=0.064N
Logistic regression tests	P=0.122N	P=0.066N	P=0.512N	P=0.063N
Cochran-Armitage test	P=0.122N			
Fisher exact test		P=0.061N	P=0.511N	P=0.059N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	6/51 (12%)	4/50 (8%)	6/50 (12%)	4/51 (8%)
Adjusted rates	13.8%	8.5%	15.8%	9.2%
Terminal rates	5/42 (12%)	3/46 (7%)	6/38 (16%)	3/42 (7%)
First incidence (days)	620	720	729 (T)	689
Life table tests	P=0.421N	P=0.318N	P=0.552	P=0.368N
Logistic regression tests	P=0.396N	P=0.357N	P=0.603	P=0.358N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.383N	P=0.606	P=0.370N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	2/48 (4%)	3/46 (7%)	6/50 (12%)	5/49 (10%)
Adjusted rates	5.1%	6.7%	15.8%	12.5%
Terminal rates	2/39 (5%)	2/42 (5%)	6/38 (16%)	5/40 (13%)
First incidence (days)	729 (T)	712	729 (T)	729 (T)
Life table tests	P=0.202	P=0.537	P=0.125	P=0.226
Logistic regression tests	P=0.206	P=0.528	P=0.125	P=0.226
Cochran-Armitage test	P=0.223			
Fisher exact test		P=0.480	P=0.148	P=0.226
Skin (Subcutaneous Tissue): Neurofibrosarcoma				
Overall rates	1/51 (2%)	0/50 (0%)	3/50 (6%)	0/51 (0%)
Adjusted rates	2.2%	0.0%	6.2%	0.0%
Terminal rates	0/42 (0%)	0/46 (0%)	0/38 (0%)	0/42 (0%)
First incidence (days)	696	–	409	–
Life table tests	P=0.448N	P=0.483N	P=0.304	P=0.500N
Logistic regression tests	P=0.496N	P=0.523N	P=0.311	P=0.503N
Cochran-Armitage test	P=0.446N			
Fisher exact test		P=0.505N	P=0.301	P=0.500N
Skin (Subcutaneous Tissue): Neurofibrosarcoma or Fibrosarcoma				
Overall rates	3/51 (6%)	0/50 (0%)	3/50 (6%)	0/51 (0%)
Adjusted rates	6.5%	0.0%	6.2%	0.0%
Terminal rates	0/42 (0%)	0/46 (0%)	0/38 (0%)	0/42 (0%)
First incidence (days)	607	–	409	–
Life table tests	P=0.198N	P=0.111N	P=0.648	P=0.123N
Logistic regression tests	P=0.208N	P=0.148N	P=0.663N	P=0.129N
Cochran-Armitage test	P=0.191N			
Fisher exact test		P=0.125N	P=0.652	P=0.121N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	2/50 (4%)	1/50 (2%)	0/49 (0%)	5/51 (10%)
Adjusted rates	4.8%	2.2%	0.0%	11.9%
Terminal rates	2/42 (5%)	1/46 (2%)	0/37 (0%)	5/42 (12%)
First incidence (days)	729 (T)	729 (T)	–	729 (T)
Life table tests	P=0.037	P=0.468N	P=0.267N	P=0.216
Logistic regression tests	P=0.037	P=0.468N	P=0.267N	P=0.216
Cochran-Armitage test	P=0.042			
Fisher exact test		P=0.500N	P=0.253N	P=0.226
All Organs: Hemangiosarcoma				
Overall rates	2/51 (4%)	4/50 (8%)	0/50 (0%)	3/51 (6%)
Adjusted rates	4.8%	8.7%	0.0%	6.7%
Terminal rates	2/42 (5%)	4/46 (9%)	0/38 (0%)	2/42 (5%)
First incidence (days)	729 (T)	729 (T)	–	631
Life table tests	P=0.541	P=0.380	P=0.261N	P=0.506
Logistic regression tests	P=0.557	P=0.380	P=0.261N	P=0.505
Cochran-Armitage test	P=0.559			
Fisher exact test		P=0.329	P=0.252N	P=0.500

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	3/51 (6%)	4/50 (8%)	0/50 (0%)	3/51 (6%)
Adjusted rates	7.1%	8.7%	0.0%	6.7%
Terminal rates	3/42 (7%)	4/46 (9%)	0/38 (0%)	2/42 (5%)
First incidence (days)	729 (T)	729 (T)	–	631
Life table tests	P=0.564N	P=0.550	P=0.139N	P=0.657N
Logistic regression tests	P=0.548N	P=0.550	P=0.139N	P=0.656N
Cochran-Armitage test	P=0.545N			
Fisher exact test		P=0.489	P=0.125N	P=0.661N
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, or Mixed)				
Overall rates	15/51 (29%)	17/50 (34%)	21/50 (42%)	13/51 (25%)
Adjusted rates	33.0%	37.0%	47.4%	28.8%
Terminal rates	12/42 (29%)	17/46 (37%)	15/38 (39%)	10/42 (24%)
First incidence (days)	323	729 (T)	554	676
Life table tests	P=0.318N	P=0.532	P=0.105	P=0.412N
Logistic regression tests	P=0.256N	P=0.373	P=0.132	P=0.408N
Cochran-Armitage test	P=0.256N			
Fisher exact test		P=0.389	P=0.133	P=0.412N
All Organs: Benign Neoplasms				
Overall rates	21/51 (41%)	24/50 (48%)	17/50 (34%)	25/51 (49%)
Adjusted rates	48.7%	49.0%	42.1%	55.4%
Terminal rates	20/42 (48%)	21/46 (46%)	15/38 (39%)	22/42 (52%)
First incidence (days)	607	701	554	473
Life table tests	P=0.235	P=0.504	P=0.400N	P=0.279
Logistic regression tests	P=0.288	P=0.466	P=0.298N	P=0.311
Cochran-Armitage test	P=0.301			
Fisher exact test		P=0.312	P=0.295N	P=0.275
All Organs: Malignant Neoplasms				
Overall rates	23/51 (45%)	23/50 (46%)	26/50 (52%)	21/51 (41%)
Adjusted rates	46.9%	48.9%	55.0%	43.6%
Terminal rates	16/42 (38%)	22/46 (48%)	17/38 (45%)	15/42 (36%)
First incidence (days)	323	679	409	447
Life table tests	P=0.423N	P=0.427N	P=0.256	P=0.420N
Logistic regression tests	P=0.339N	P=0.512	P=0.312	P=0.436N
Cochran-Armitage test	P=0.338N			
Fisher exact test		P=0.543	P=0.310	P=0.421N
All Organs: Benign or Malignant Neoplasms				
Overall rates	37/51 (73%)	37/50 (74%)	37/50 (74%)	36/51 (71%)
Adjusted rates	75.5%	74.0%	77.0%	72.0%
Terminal rates	30/42 (71%)	33/46 (72%)	27/38 (71%)	28/42 (67%)
First incidence (days)	323	679	409	447
Life table tests	P=0.534	P=0.335N	P=0.356	P=0.487N
Logistic regression tests	P=0.416N	P=0.575N	P=0.521	P=0.478N
Cochran-Armitage test	P=0.418N			
Fisher exact test		P=0.524	P=0.524	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

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

TABLE D4
Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	**Carcinoma**	**Adenoma or Carcinoma**
Historical Incidence at Battelle Columbus Laboratories			
2,4-Dichlorophenol	1/49	0/49	1/49
5,5-Diphenylhydantoin	4/47	0/47	4/47
Dowicide EC-7 Pentachlorophenol	3/34	0/34	3/34
Ethylene thiourea	0/50	0/50	0/50
Polybrominated biphenyls (Firemaster FF-1®)	0/49	0/49	0/49
Manganese (II) sulfate monohydrate	2/50	0/50	2/50
Technical Grade Pentachlorophenol	0/33	0/33	0/33
Triamterene	1/49	1/49	2/49
Triamterene	0/50	0/50	0/50
Overall Historical Incidence			
Total	27/1,099 (2.5%)	2/1,099 (0.2%)	29/1,099 (2.6%)
Standard deviation	2.9%	0.6%	3.0%
Range	0%-9%	0%-2%	0%-9%

[a] Data as of 17 December 1991

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Disposition Summary				
Animals initially in study	70	70	70	70
9-Month interim evaluation	10	10	10	10
15-Month interim evaluation	9	10	9	9
Early deaths				
Accidental deaths	1			
Moribund	6	4	6	4
Natural deaths	2		6	5
Survivors				
Terminal sacrifice	42	46	38	42
Missing			1	
Animals examined microscopically	70	61	62	70
9-Month Interim Evaluation				
Alimentary System				
Stomach, forestomach	(10)			(9)
Hyperplasia, focal, squamous				1 (11%)
Cardiovascular System				
None				
Endocrine System				
Thyroid gland	(10)		(1)	(10)
Follicle, cyst	1 (10%)			
Follicle, dilatation			1 (100%)	7 (70%)
General Body System				
None				
Genital System				
Ovary	(10)	(1)	(1)	(9)
Follicle, cyst		1 (100%)	1 (100%)	
Periovarian tissue, cyst	1 (10%)			
Uterus	(10)			(9)
Endometrium, hyperplasia, cystic, glandular	10 (100%)			9 (100%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
9-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
None				
Special Senses System				
None				
Urinary System				
None				
15-Month Interim Evaluation				
Alimentary System				
Liver	(9)	(10)	(9)	(9)
Basophilic focus			1 (11%)	
Eosinophilic focus				1 (11%)
Inflammation, acute, focal		2 (20%)		
Vacuolization cytoplasmic	1 (11%)	1 (10%)		
Stomach, forestomach	(9)		(1)	(9)
Hyperplasia, focal, squamous			1 (100%)	1 (11%)
Inflammation, chronic active				1 (11%)
Cardiovascular System				
None				
Endocrine System				
Islets, pancreatic	(9)			(9)
Hyperplasia				1 (11%)
Thyroid gland	(9)		(2)	(9)
Follicle, cyst	2 (22%)		2 (100%)	
Follicle, dilatation				5 (56%)
General Body System				
None				
Genital System				
Ovary	(8)		(2)	(9)
Follicle, cyst	1 (13%)		2 (100%)	2 (22%)
Periovarian tissue, cyst				2 (22%)
Uterus	(9)	(2)	(4)	(9)
Endometrium, hyperplasia, cystic, glandular	8 (89%)	2 (100%)	4 (100%)	8 (89%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(9)			(9)
Perivascular, inflammation, chronic active	1 (11%)			
Special Senses System				
None				
Urinary System				
Kidney	(9)			(9)
Renal tubule, regeneration				1 (11%)
2-Year Study				
Alimentary System				
Liver	(51)	(50)	(50)	(51)
Basophilic focus	1 (2%)	7 (14%)	2 (4%)	5 (10%)
Clear cell focus		5 (10%)	2 (4%)	
Congestion				1 (2%)
Cytomegaly, multifocal	1 (2%)			
Eosinophilic focus	8 (16%)	8 (16%)	3 (6%)	3 (6%)
Hepatodiaphragmatic nodule			2 (4%)	
Infarct		1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, chronic active		1 (2%)	1 (2%)	1 (2%)
Mixed cell focus				3 (6%)
Vacuolization cytoplasmic	5 (10%)	2 (4%)	7 (14%)	4 (8%)
Hepatocyte, atrophy	1 (2%)			
Kupffer cell, hyperplasia	1 (2%)			
Mesentery	(8)	(3)	(1)	
Fat, inflammation, chronic active	6 (75%)	2 (67%)	1 (100%)	
Pancreas	(51)	(50)	(50)	(51)
Inflammation, chronic active				1 (2%)
Acinus, atrophy	1 (2%)	4 (8%)	2 (4%)	
Duct, cyst		2 (4%)	1 (2%)	1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Salivary glands	(51)	(50)	(50)	(50)
Infiltration cellular, lymphocyte	1 (2%)			
Stomach, forestomach	(51)	(50)	(49)	(50)
Erosion, focal				2 (4%)
Hyperplasia, focal, squamous	1 (2%)	3 (6%)	3 (6%)	9 (18%)
Inflammation, chronic active		1 (2%)		3 (6%)
Ulcer	2 (4%)		1 (2%)	3 (6%)
Stomach, glandular	(51)	(50)	(50)	(49)
Degeneration	1 (2%)			
Inflammation, chronic	1 (2%)			
Mineralization			1 (2%)	
Ulcer			2 (4%)	
Cardiovascular System				
Heart	(51)	(50)	(50)	(51)
Inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal gland	(51)	(50)	(50)	(51)
Corticomedullary junction, vacuolization cytoplasmic			1 (2%)	
Adrenal gland, cortex	(51)	(50)	(48)	(51)
Hyperplasia	4 (8%)	7 (14%)	6 (13%)	5 (10%)
Hypertrophy	2 (4%)	4 (8%)	6 (13%)	5 (10%)
Mineralization			1 (2%)	
Vacuolization cytoplasmic	2 (4%)		1 (2%)	
Adrenal gland, medulla	(51)	(50)	(48)	(51)
Cyst	1 (2%)			
Hyperplasia	1 (2%)	2 (4%)		
Pituitary gland	(48)	(46)	(50)	(49)
Pars distalis, cyst	3 (6%)	3 (7%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia	6 (13%)	7 (15%)	4 (8%)	10 (20%)
Thyroid gland	(50)	(50)	(49)	(51)
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, chronic active	1 (2%)	2 (4%)	3 (6%)	
Inflammation, granulomatous			1 (2%)	
Follicle, cyst	15 (30%)	12 (24%)	7 (14%)	7 (14%)
Follicle, dilatation	1 (2%)	5 (10%)	11 (22%)	24 (47%)
Follicular cell, hyperplasia, diffuse	1 (2%)	1 (2%)		
Follicular cell, hyperplasia, focal	3 (6%)	15 (30%)	27 (55%)	43 (84%)
General Body System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Genital System				
Ovary				
Atrophy	2 (4%)			
Fibrosis				1 (2%)
Inflammation, chronic active	1 (2%)			
Mineralization		1 (2%)		
Thrombosis			1 (2%)	
Bilateral, atrophy	1 (2%)			
Bilateral, follicle, cyst	1 (2%)			1 (2%)
Follicle, cyst	18 (35%)	18 (36%)	15 (30%)	12 (24%)
Periovarian tissue, cyst	2 (4%)	2 (4%)	3 (6%)	7 (14%)
Periovarian tissue, inflammation, chronic active				1 (2%)
Rete ovarii, cyst				1 (2%)
Uterus	(51)	(50)	(50)	(51)
Hemorrhage	1 (2%)			
Cervix, inflammation, chronic active				1 (2%)
Endometrium, angiectasis				1 (2%)
Endometrium, hyperplasia, cystic, glandular	48 (94%)	47 (94%)	46 (92%)	49 (96%)
Endometrium, thrombosis			1 (2%)	
Lymphatic, cyst			1 (2%)	
Hematopoietic System				
Bone marrow	(51)	(50)	(50)	(51)
Femoral, atrophy	1 (2%)			1 (2%)
Lymph node	(51)	(50)	(49)	(50)
Mediastinal, infiltration cellular, histiocyte			1 (2%)	
Lymph node, mandibular	(49)	(50)	(47)	(46)
Depletion lymphoid			1 (2%)	
Infiltration cellular, histiocyte		2 (4%)		
Lymph node, mesenteric	(48)	(48)	(44)	(45)
Inflammation, chronic active				1 (2%)
Spleen	(51)	(50)	(50)	(51)
Depletion lymphoid	1 (2%)		1 (2%)	
Hematopoietic cell proliferation	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Inflammation, chronic active				1 (2%)
Necrosis			1 (2%)	
Thrombosis				1 (2%)
Thymus	(49)	(49)	(47)	(46)
Depletion lymphoid	3 (6%)	3 (6%)	3 (6%)	3 (7%)
Inflammation, chronic active				1 (2%)
Integumentary System				
Mammary gland	(43)	(45)	(39)	(37)
Hyperplasia, cystic		1 (2%)	1 (3%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(51)	(50)	(50)	(51)
Abscess		1 (2%)		
Acanthosis		1 (2%)		
Alopecia	4 (8%)	2 (4%)	3 (6%)	3 (6%)
Ulcer		4 (8%)		
Subcutaneous tissue, inflammation, chronic active		4 (8%)		1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)			
Back, inflammation, chronic active	1 (100%)			
Nervous System				
Brain	(51)	(50)	(50)	(51)
Compression				1 (2%)
Hemorrhage				1 (2%)
Hydrocephalus		1 (2%)		1 (2%)
Cerebellum, cyst epithelial inclusion			1 (2%)	
Spinal cord	(2)			
Lumbar, degeneration	1 (50%)			
Respiratory System				
Lung	(51)	(50)	(50)	(51)
Inflammation, chronic active	2 (4%)			2 (4%)
Alveolar epithelium, hyperplasia		1 (2%)	2 (4%)	1 (2%)
Special Senses System				
Eye				(1)
Cornea, inflammation, chronic active				1 (100%)
Harderian gland	(6)	(3)	(2)	
Hyperplasia	3 (50%)			
Urinary System				
Kidney	(51)	(50)	(50)	(51)
Nephropathy	41 (80%)	36 (72%)	33 (66%)	31 (61%)
Pelvis, inflammation, chronic active				1 (2%)
Renal tubule, cytomegaly				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 Mortelmans *et al.* (1986). Manganese (II) sulfate monohydrate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with *Salmonella typhimurium* tester strains (TA97, TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of manganese (II) sulfate monohydrate. The high dose selected was 10,000 µg/plate. 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 that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to the judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1987). Manganese (II) sulfate monohydrate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of manganese (II) sulfate monohydrate; 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 manganese (II) sulfate monohydrate in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing manganese (II) sulfate monohydrate 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 Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with manganese (II) sulfate monohydrate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no manganese (II) sulfate monohydrate, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. 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 at the two highest doses in the absence of S9, 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; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P \leq 0.05$) 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 manganese (II) sulfate monohydrate for 10 to 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with manganese (II) sulfate monohydrate and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; because cell cycle delay was anticipated in the absence of S9, the incubation period was extended.

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 ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive. A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway *et al.*, 1987).

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assay for induction of sex-linked recessive lethal (SLRL) mutations was performed with adult flies as described by Valencia *et al.* (1985). Manganese (II) sulfate monohydrate was supplied as a coded aliquot by 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, manganese (II) sulfate monohydrate was retested by injection into adult males.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament, and the tip is broken off to allow delivery of the test solution. Injection is 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 which automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, is performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of manganese (II) sulfate monohydrate at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of manganese (II) sulfate monohydrate in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of manganese (II) sulfate monohydrate dissolved in 0.7% saline and 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). F_1 heterozygous females were mated with their siblings and 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 results 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 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 is considered positive if the P value is less than 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value is less than 0.05 and the frequency in the treatment group is greater than 0.15%. A test is considered to be inconclusive if (a) the P value is between 0.05 and 0.01 but the frequency in the treatment group is between 0.10% and 0.15% or (b) the P value is between 0.10 and 0.05 but the frequency in the treatment group is greater than 0.10%. A test is considered negative if the P value is greater than 0.10 or if the frequency in the treatment group is less than 0.10%.

RESULTS

Manganese (II) sulfate monohydrate (100 to 10,000 µg/plate), tested in two laboratories, was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537. All tests were performed with a preincubation protocol, with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9.

In cytogenetic tests with CHO cells, manganese (II) sulfate monohydrate induced SCEs with and without S9 activation. Two of the three positive responses obtained in the absence of S9 required delayed cell culture harvest to offset severe manganese (II) sulfate monohydrate-induced cytotoxicity; with S9, all positive responses were achieved with normal harvest times. Manganese (II) sulfate monohydrate also induced chromosomal aberrations in CHO cells in the absence of S9; as with the SCE test, the harvest time was extended to allow sufficient cells to accumulate for analysis. Increases in the percentage of cells with aberrations were not well correlated with the dose of manganese (II) sulfate monohydrate and occurred within a rather limited range (176 to 300 µg/mL). In the presence of S9, no significant increase in chromosomal aberrations was observed.

Manganese (II) sulfate monohydrate did not induce SLRL mutations in germ cells of adult male *D. melanogaster* treated with 12,500 ppm in feed or 1,000 ppm administered by injection.

TABLE E1
Mutagenicity of Manganese (II) Sulfate Monohydrate in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at SRI, Inc.							
TA100	0	114 ± 6.7	104 ± 6.1	101 ± 3.5	105 ± 5.2	113 ± 1.5	113 ± 7.1
	100	113 ± 6.9	115 ± 7.2	108 ± 3.9	103 ± 11.4	110 ± 2.8	107 ± 8.2
	333	108 ± 5.8	113 ± 14.2	106 ± 9.4	106 ± 13.4	113 ± 5.0	110 ± 10.4
	1,000	110 ± 9.3	118 ± 12.9	119 ± 5.3	115 ± 7.8	105 ± 5.5	126 ± 11.5
	3,333	108 ± 3.7	117 ± 5.5	111 ± 11.4	114 ± 6.4	127 ± 8.2	98 ± 1.2
	10,000	89 ± 6.8	86 ± 5.8	105 ± 3.5	78 ± 1.5	84 ± 3.2	88 ± 5.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control[c]	364 ± 3.3	334 ± 24.2	342 ± 27.0	1,394 ± 23.9	384 ± 8.7	894 ± 7.1
TA1535							
	0	17 ± 1.2	21 ± 1.8	12 ± 2.0	9 ± 2.1	10 ± 2.6	9 ± 2.5
	100	21 ± 2.9	25 ± 4.0	12 ± 1.7	10 ± 1.2	12 ± 2.9	10 ± 2.2
	333	24 ± 5.0	21 ± 4.4	8 ± 1.9	9 ± 1.8	10 ± 2.3	10 ± 1.2
	1,000	18 ± 1.7	28 ± 1.9	7 ± 0.9	7 ± 1.2	6 ± 0.7	9 ± 1.7
	3,333	26 ± 4.6	18 ± 0.9	8 ± 1.2	6 ± 1.2	12 ± 1.5	7 ± 0.6
	10,000	23 ± 3.8	14 ± 2.6	7 ± 1.5	8 ± 0.9	8 ± 1.5	8 ± 0.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	455 ± 23.8	370 ± 17.9	448 ± 27.6	359 ± 26.0	150 ± 5.0	191 ± 5.5
TA1537							
	0	10 ± 1.2	6 ± 1.5	7 ± 1.0	6 ± 0.9	5 ± 0.9	6 ± 0.9
	100	5 ± 1.5	7 ± 1.7	8 ± 2.3	8 ± 1.9	7 ± 0.3	6 ± 1.9
	333	6 ± 0.3	8 ± 2.3	11 ± 0.7	7 ± 1.5	7 ± 0.9	7 ± 0.9
	1,000	7 ± 2.3	5 ± 0.9	9 ± 1.5	7 ± 1.5	10 ± 1.5	8 ± 0.7
	3,333	4 ± 1.9	6 ± 1.3	9 ± 1.0	3 ± 0.9	6 ± 1.2	7 ± 0.3
	10,000	7 ± 0.9	5 ± 0.3	6 ± 1.5	5 ± 2.0	5 ± 0.3	5 ± 1.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	150 ± 6.2	151 ± 12.4	243 ± 18.6	213 ± 20.1	141 ± 4.6	236 ± 15.3
TA98							
	0	24 ± 6.0	14 ± 1.2	19 ± 5.3	25 ± 3.8	22 ± 1.3	19 ± 0.7
	100	14 ± 1.2	14 ± 2.7	25 ± 0.6	15 ± 2.2	22 ± 2.3	17 ± 0.3
	333	16 ± 4.0	19 ± 3.7	21 ± 1.5	16 ± 2.2	19 ± 0.9	16 ± 1.2
	1,000	15 ± 1.8	14 ± 1.2	23 ± 3.2	18 ± 1.3	26 ± 2.3	19 ± 4.4
	3,333	13 ± 0.9	12 ± 0.9	21 ± 0.7	17 ± 1.7	25 ± 4.9	17 ± 2.6
	10,000	12 ± 1.5	13 ± 1.5	24 ± 0.6	14 ± 1.9	17 ± 2.1	10 ± 0.3
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control	871 ± 13.9	975 ± 28.7	611 ± 71.3	1,362 ± 95.8	297 ± 38.2	849 ± 44.4

TABLE E1
Mutagenicity of Manganese (II) Sulfate Monohydrate in *Salmonella typhimurium* (continued)

Strain	Dose (µg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
Study performed at Microbiological Associates:							
TA100							
	0	108 ± 9.0	92 ± 4.7	97 ± 7.0	99 ± 1.9	115 ± 4.1	106 ± 9.9
	100	112 ± 6.5	84 ± 3.4	112 ± 6.7	84 ± 11.0	91 ± 3.2	90 ± 6.8
	333	124 ± 4.2[d]	80 ± 3.7	95 ± 8.4	89 ± 5.1	80 ± 4.2	83 ± 2.4
	1,000	112 ± 8.7[d]	77 ± 2.4	106 ± 1.9	92 ± 1.5	90 ± 1.5	91 ± 8.7
	3,333	112 ± 9.7[d]	70 ± 5.0	93 ± 3.2[d]	87 ± 3.9[d]	85 ± 2.6[d]	77 ± 6.0[d]
	10,000	95 ± 8.5[d]	68 ± 2.3[d]	77 ± 6.4[d]	61 ± 3.0[d]	74 ± 6.1[d]	66 ± 2.8[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		473 ± 9.6	293 ± 17.3	378 ± 14.7	260 ± 10.9	862 ± 33.7	517 ± 24.1
TA1535							
	0	32 ± 2.1	7 ± 1.2	7 ± 1.7	5 ± 1.2	11 ± 1.3	4 ± 0.9
	100	33 ± 1.5	7 ± 2.2	13 ± 0.9	6 ± 1.9	10 ± 1.8	6 ± 1.0
	333	22 ± 3.5	5 ± 0.9	8 ± 0.7	4 ± 0.7	9 ± 0.3	6 ± 0.6
	1,000	22 ± 1.2	6 ± 0.9	11 ± 1.2	5 ± 1.7	8 ± 1.2	7 ± 0.6
	3,333	16 ± 4.4[d]	6 ± 0.3	7 ± 1.9[d]	6 ± 0.6[d]	9 ± 1.2[d]	7 ± 2.2[d]
	10,000	16 ± 3.2[d]	2 ± 0.6[d]	5 ± 1.3[d]	2 ± 1.2[d]	6 ± 1.0[d]	4 ± 0.9[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		284 ± 13.0	123 ± 15.9	54 ± 6.7	58 ± 4.9	196 ± 2.7	83 ± 8.9
TA97							
	0	113 ± 12.1	75 ± 2.7	131 ± 10.4	128 ± 5.2	160 ± 5.2	138 ± 5.7
	100	123 ± 4.6	72 ± 3.6	160 ± 10.7	98 ± 6.6	122 ± 3.5	112 ± 3.9
	333	111 ± 4.9	83 ± 2.0	125 ± 6.0	100 ± 4.9	118 ± 3.5	99 ± 4.4
	1,000	125 ± 6.5[d]	84 ± 7.9	164 ± 2.9	110 ± 7.5	133 ± 3.6	96 ± 8.7
	3,333	135 ± 5.9[d]	77 ± 5.0[d]	167 ± 5.8[d]	93 ± 6.4	164 ± 7.6[d]	108 ± 2.3[d]
	10,000	123 ± 12.7[d]	80 ± 9.3[d]	110 ± 5.2[d]	77 ± 4.7[d]	115 ± 7.7[d]	97 ± 7.7[d]
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		405 ± 10.5	595 ± 27.6	295 ± 7.6	542 ± 19.7	1,313 ± 21.1	411 ± 6.6
TA98							
	0	18 ± 2.2	12 ± 1.5	28 ± 1.0	18 ± 1.5	25 ± 0.9	18 ± 3.7
	100	18 ± 2.7	10 ± 1.2	21 ± 2.2	10 ± 2.4	21 ± 2.2	17 ± 1.5
	333	12 ± 1.2	9 ± 1.2	24 ± 1.2	12 ± 2.3	23 ± 4.7	16 ± 3.6
	1,000	15 ± 2.3	9 ± 1.0	21 ± 4.7	16 ± 1.5	23 ± 3.5	16 ± 2.3
	3,333	13 ± 2.3	14 ± 2.4	14 ± 2.3	12 ± 2.0	19 ± 1.3[d]	15 ± 0.9[d]
	10,000	20 ± 1.9[d]	9 ± 1.8[d]	14 ± 1.2	8 ± 2.0[d]	19 ± 3.5[d]	6 ± 1.5[d]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		149 ± 1.9	234 ± 12.0	148 ± 10.4	73 ± 8.1	251 ± 21.5	192 ± 10.0

[a] The detailed protocol and these data are presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± the standard error from three plates.
[c] 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 and TA97.
[d] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Manganese (II) Sulfate Monohydrate[a]

Compound	Dose µg/mL	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Summary: Positive								
Distilled water		50	1,036	421	0.40	8.4	25.5	
Mitomycin-C	0.001	50	1,018	616	0.60	12.3	25.5	48.90
	0.010	5	104	250	2.40	50.0	25.5	491.54
Manganese (II) sulfate monohydrate								
	5.0	50	1,036	536	0.51	10.7	25.5	27.32*
	16.7	50	1,024	657	0.64	13.1	34.0[c]	57.89*
	50.0	50	1,026	686	0.66	13.7	34.0[c]	64.53*
								P≤0.001[d]
+S9								
Trial 1								
Summary: Positive								
Distilled water		50	1,021	462	0.45	9.2	25.5	
Cyclophosphamide								
	15.0	25	512	559	1.09	22.4	25.5	141.28
Manganese (II) sulfate monohydrate								
	200	50	1,033	508	0.49	10.2	25.5	8.68
	245	50	1,021	500	0.48	10.0	25.5	8.23
	298	12	239	133	0.55	11.1	25.5	22.98*
	350	50	1,012	683	0.67	13.7	25.5	49.15*
								P≤0.001
Trial 2								
Summary: Positive								
Distilled water		50	1,036	420	0.40	8.4	25.5	
Cyclophosphamide								
	0.3	50	1,027	534	0.51	10.7	25.5	28.26
	2.0	5	104	122	1.17	24.4	25.5	189.36
Manganese (II) sulfate monohydrate								
	300	50	1,023	580	0.56	11.6	25.5	39.85*
	332	50	1,020	527	0.51	10.5	25.5	27.44*
	350	50	1,023	596	0.58	11.9	25.5	43.71*
								P≤0.001

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Manganese (II) Sulfate Monohydrate

* Positive (>20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE=sister chromatid exchange; BrdU=bromodeoxyuridine.
[b] SCEs/chromosome of culture exposed to manganese (II) sulfate monohydrate relative to those of culture exposed to solvent
[c] Because manganese (II) sulfate monohydrate induced a delay in the cell division cycle, harvest times were extended to maximize the proportion of second division cells available for analysis.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Manganese (II) Sulfate Monohydrate[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: 20.0 hours[b] Summary: Positive					**Trial 1** - Harvest time: 10.5 hours Summary: Negative				
Distilled water					Distilled water				
	100	1	0.01	1.0		100	0	0.00	0.0
Mitomycin-C					Cyclophosphamide				
0.0620	50	50	1.00	58.0	25	50	9	0.18	16.0
Manganese (II) sulfate monohydrate					Manganese (II) sulfate monohydrate				
141	100	7	0.07	3.0	400	100	1	0.01	1.0
200	100	12	0.12	11.0*	450	100	3	0.03	3.0
300	100	8	0.08	8.0*	500	100	2	0.02	2.0
				P=0.003[c]					P=0.068
Trial 2 - Harvest time: 19 hours[b] Summary: Positive									
Distilled water									
	100	0	0.00	0.0					
Mitomycin-C									
0.620	50	11	0.22	18.0					
Manganese (II) sulfate monohydrate									
150	100	2	0.02	2.0					
176	100	6	0.06	6.0*					
200	100	8	0.08	5.0*					
				P=0.007					

* Significant increase ($P \leq 0.05$)
[a] Study performed at Litton Bionetics, Inc. Abs=aberrations.
[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient metaphase cells at harvest.
[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

TABLE E4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Manganese (II) Sulfate Monohydrate[a]

Route of Exposure	Dose (ppm)	Incidence of of Deaths (%)	Incidence of of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Total[b]
Injection	1,000	0	0	1/2,186	2/2,043	0/1,979	3/6,208 (0.05%)
	0			1/1,956	4/1,955	1/1,780	6/5,691 (0.11%)
Feeding	12,500	17	11	3/2,830	1/2,417	1/2,076	5/7,323 (0.07%)
	0			2/2,343	0/2,039	2/1,721	4/6,103 (0.07%)

[a] Study performed at Bowling Green State University. A detailed protocol of the sex-linked recessive lethal assay and these data are presented in Valencia *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 14-Day Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	241 ± 12	235 ± 5	242 ± 13	235 ± 6	243 ± 6	210 ± 6*
Brain						
Absolute	1.654 ± 0.089	1.718 ± 0.025	1.640 ± 0.101	1.674 ± 0.054	1.732 ± 0.077	1.748 ± 0.034
Relative	6.95 ± 0.51	7.32 ± 0.08	6.85 ± 0.57	7.14 ± 0.23	7.15 ± 0.37	8.35 ± 0.21*
Heart						
Absolute	0.692 ± 0.038	0.668 ± 0.031	0.728 ± 0.049	0.678 ± 0.022	0.700 ± 0.016	0.602 ± 0.019
Relative	2.88 ± 0.05	2.84 ± 0.07	3.00 ± 0.09	2.89 ± 0.05	2.88 ± 0.03	2.87 ± 0.04
R. Kidney						
Absolute	0.880 ± 0.048	0.844 ± 0.037	0.870 ± 0.057	0.838 ± 0.019	0.884 ± 0.023	0.802 ± 0.018
Relative	3.66 ± 0.04	3.59 ± 0.08	3.58 ± 0.07	3.57 ± 0.03	3.64 ± 0.02	3.83 ± 0.07
Liver						
Absolute	8.988 ± 0.553	9.028 ± 0.324	9.092 ± 0.402	8.114 ± 0.256	8.598 ± 0.141	7.528 ± 0.264**
Relative	37.27 ± 0.48	38.37 ± 0.58	37.62 ± 0.57	34.57 ± 0.82*	35.41 ± 0.40*	35.87 ± 0.57*
Lungs						
Absolute	1.004 ± 0.058	1.082 ± 0.039	1.176 ± 0.095	1.030 ± 0.035	1.030 ± 0.046	1.024 ± 0.045
Relative	4.17 ± 0.11	4.61 ± 0.14	4.83 ± 0.16*	4.39 ± 0.13	4.24 ± 0.15	4.89 ± 0.20*
L. Testis						
Absolute	1.256 ± 0.063	1.225 ± 0.026[b]	1.256 ± 0.043	1.236 ± 0.025	1.272 ± 0.029	1.234 ± 0.044
Relative	5.22 ± 0.03	5.17 ± 0.04	5.21 ± 0.14	5.27 ± 0.08	5.24 ± 0.07	5.89 ± 0.17**
Thymus						
Absolute	0.261 ± 0.014	0.266 ± 0.033	0.272 ± 0.013	0.241 ± 0.013	0.252 ± 0.015	0.241 ± 0.011
Relative	1.10 ± 0.08	1.13 ± 0.14	1.13 ± 0.08	1.03 ± 0.05	1.04 ± 0.07	1.16 ± 0.08
Female						
n	5	5	5	5	5	5
Necropsy body wt	165 ± 4	169 ± 6	157 ± 3	163 ± 6	166 ± 4	153 ± 5
Brain						
Absolute	1.660 ± 0.024	1.684 ± 0.038	1.662 ± 0.036	1.590 ± 0.069	1.660 ± 0.048	1.672 ± 0.020
Relative	10.09 ± 0.22	9.99 ± 0.35	10.61 ± 0.36	9.77 ± 0.42	10.03 ± 0.39	10.94 ± 0.28
Heart						
Absolute	0.522 ± 0.019	0.556 ± 0.018	0.502 ± 0.015	0.492 ± 0.021	0.530 ± 0.013	0.482 ± 0.024
Relative	3.17 ± 0.08	3.29 ± 0.08	3.20 ± 0.09	3.01 ± 0.05	3.19 ± 0.04	3.14 ± 0.06
R. Kidney						
Absolute	0.604 ± 0.017	0.620 ± 0.030	0.556 ± 0.019	0.568 ± 0.018	0.610 ± 0.034	0.566 ± 0.022
Relative	3.67 ± 0.09	3.66 ± 0.06	3.54 ± 0.06	3.48 ± 0.08	3.67 ± 0.13	3.69 ± 0.04
Liver						
Absolute	6.018 ± 0.212	5.634 ± 0.278	5.274 ± 0.260	5.228 ± 0.297	5.586 ± 0.122	5.132 ± 0.197*
Relative	36.49 ± 0.70	33.26 ± 0.83	33.58 ± 1.43	31.96 ± 0.99*	33.76 ± 1.22	33.49 ± 0.95
Lungs						
Absolute	0.824 ± 0.044	0.908 ± 0.065	0.890 ± 0.044	0.816 ± 0.070	0.922 ± 0.076	0.746 ± 0.052
Relative	4.99 ± 0.21	5.35 ± 0.25	5.68 ± 0.29	4.99 ± 0.37	5.53 ± 0.38	4.85 ± 0.21
Thymus						
Absolute	0.290 ± 0.016	0.284 ± 0.019	0.241 ± 0.011	0.242 ± 0.025	0.287 ± 0.012	0.260 ± 0.020
Relative	1.76 ± 0.09	1.67 ± 0.08	1.54 ± 0.06	1.49 ± 0.18	1.73 ± 0.07	1.69 ± 0.10

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

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,600 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	301 ± 4	300 ± 5	296 ± 4	299 ± 4	296 ± 6	298 ± 11
Brain						
Absolute	1.723 ± 0.015	1.708 ± 0.013	1.731 ± 0.017	1.707 ± 0.045	1.721 ± 0.010	1.715 ± 0.029
Relative	5.73 ± 0.06	5.70 ± 0.08	5.86 ± 0.07	5.72 ± 0.16	5.84 ± 0.11	5.82 ± 0.21
Heart						
Absolute	0.720 ± 0.016	0.733 ± 0.019	0.744 ± 0.009	0.739 ± 0.021	0.742 ± 0.023	0.710 ± 0.014
Relative	2.39 ± 0.05	2.44 ± 0.05	2.52 ± 0.02	2.47 ± 0.08	2.51 ± 0.04	2.40 ± 0.08
R. Kidney						
Absolute	0.899 ± 0.016	0.858 ± 0.014	0.852 ± 0.015	0.904 ± 0.028	0.861 ± 0.019	0.892 ± 0.025
Relative	2.99 ± 0.05	2.86 ± 0.03	2.88 ± 0.04	3.02 ± 0.08	2.91 ± 0.04	3.01 ± 0.09
Liver						
Absolute	10.688 ± 0.282	9.535 ± 0.205**	9.129 ± 0.165**	9.441 ± 0.211**	8.950 ± 0.274**	9.014 ± 0.274**
Relative	35.49 ± 0.71	31.78 ± 0.50**	30.85 ± 0.25**	31.57 ± 0.55**	30.25 ± 0.49**	30.43 ± 1.00**
Lungs						
Absolute	1.164 ± 0.037	1.073 ± 0.031	1.080 ± 0.019	1.111 ± 0.042	1.325 ± 0.060*	1.011 ± 0.032*
Relative	3.86 ± 0.10	3.57 ± 0.08	3.65 ± 0.06	3.72 ± 0.15	4.49 ± 0.21**	3.42 ± 0.13
L. Testis						
Absolute	1.292 ± 0.033	1.414 ± 0.103	1.294 ± 0.021	1.315 ± 0.011	1.245 ± 0.031	1.290 ± 0.019
Relative	4.29 ± 0.10	4.74 ± 0.39	4.38 ± 0.08	4.40 ± 0.06	4.22 ± 0.11	4.36 ± 0.11
Thymus						
Absolute	0.146 ± 0.017	0.144 ± 0.016	0.109 ± 0.013	0.170 ± 0.021	0.174 ± 0.018	0.118 ± 0.018
Relative	0.48 ± 0.05	0.48 ± 0.05	0.37 ± 0.04	0.56 ± 0.07	0.58 ± 0.06	0.39 ± 0.05
Female						
n	10	10	10	10	10	10
Necropsy body wt	187 ± 2	182 ± 2	178 ± 3*	178 ± 2*	181 ± 1*	178 ± 3**
Brain						
Absolute	1.638 ± 0.012	1.596 ± 0.021	1.608 ± 0.017	1.613 ± 0.025	1.638 ± 0.016	1.608 ± 0.007
Relative	8.78 ± 0.10	8.76 ± 0.12	9.05 ± 0.13	9.08 ± 0.14	9.05 ± 0.10	9.05 ± 0.12
Heart						
Absolute	0.485 ± 0.015	0.478 ± 0.008	0.443 ± 0.016	0.477 ± 0.013	0.472 ± 0.011	0.465 ± 0.016
Relative	2.60 ± 0.07	2.62 ± 0.04	2.49 ± 0.07	2.68 ± 0.06	2.61 ± 0.06	2.61 ± 0.08
R. Kidney						
Absolute	0.509 ± 0.011	0.505 ± 0.014	0.498 ± 0.008	0.493 ± 0.013	0.511 ± 0.011	0.517 ± 0.015[b]
Relative	2.73 ± 0.06	2.77 ± 0.08	2.80 ± 0.04	2.77 ± 0.07	2.82 ± 0.06	2.89 ± 0.08[b]
Liver						
Absolute	5.754 ± 0.225	5.689 ± 0.119	5.343 ± 0.146	5.363 ± 0.125	5.281 ± 0.084*	5.008 ± 0.143**
Relative	30.80 ± 1.08	31.20 ± 0.53	30.04 ± 0.70	30.16 ± 0.59	29.17 ± 0.37	28.10 ± 0.52**
Lungs						
Absolute	1.006 ± 0.061	0.847 ± 0.031**	0.878 ± 0.030**	0.761 ± 0.021**	0.834 ± 0.025**	0.712 ± 0.036**
Relative	5.40 ± 0.34	4.65 ± 0.17*	4.94 ± 0.16*	4.28 ± 0.11**	4.62 ± 0.16**	4.00 ± 0.20**
Thymus						
Absolute	0.130 ± 0.011	0.117 ± 0.008	0.123 ± 0.019	0.113 ± 0.011	0.126 ± 0.013	0.121 ± 0.008
Relative	0.70 ± 0.06	0.64 ± 0.04	0.69 ± 0.11	0.63 ± 0.06	0.70 ± 0.07	0.68 ± 0.04

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	8	9	10	10
Necropsy body wt	474 ± 10	469 ± 8	468 ± 10	437 ± 6**
Brain				
Absolute	2.110 ± 0.024	2.081 ± 0.016	2.108 ± 0.031	2.104 ± 0.029
Relative	4.46 ± 0.09	4.45 ± 0.08	4.51 ± 0.06	4.82 ± 0.05**
L. Kidney				
Absolute	1.661 ± 0.052	1.613 ± 0.027	1.638 ± 0.040	1.552 ± 0.042
Relative	3.50 ± 0.05	3.44 ± 0.04	3.50 ± 0.04	3.55 ± 0.06
R. Kidney				
Absolute	1.607 ± 0.046	1.620 ± 0.033	1.616 ± 0.056	1.561 ± 0.032
Relative	3.39 ± 0.05	3.46 ± 0.04	3.44 ± 0.07	3.57 ± 0.06*
Liver				
Absolute	17.579 ± 0.371	16.861 ± 0.530	17.049 ± 0.628	16.111 ± 0.502
Relative	37.07 ± 0.31	35.90 ± 0.60	36.38 ± 0.95	36.86 ± 0.99
Female				
n	9	10	10	10
Necropsy body wt	241 ± 5	252 ± 2	251 ± 8	245 ± 4
Brain				
Absolute	2.017 ± 0.106	1.930 ± 0.024	1.910 ± 0.020	1.918 ± 0.014
Relative	8.35 ± 0.36	7.68 ± 0.11	7.66 ± 0.18	7.85 ± 0.11
L. Kidney				
Absolute	0.910 ± 0.029	0.917 ± 0.025	0.889 ± 0.041	0.894 ± 0.021
Relative	3.76 ± 0.08	3.64 ± 0.09	3.54 ± 0.11	3.65 ± 0.06
R. Kidney				
Absolute	0.909 ± 0.038	0.921 ± 0.021	0.870 ± 0.036	0.897 ± 0.024
Relative	3.75 ± 0.11	3.66 ± 0.07	3.46 ± 0.09*	3.66 ± 0.05
Liver				
Absolute	8.154 ± 0.270	8.276 ± 0.241	8.038 ± 0.304	8.227 ± 0.252
Relative	33.74 ± 0.76	32.88 ± 0.73	32.02 ± 0.69	33.57 ± 0.68

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	9	9	8
Necropsy body wt	478 ± 10	478 ± 11	498 ± 9	492 ± 10
Brain				
Absolute	2.074 ± 0.024	2.044 ± 0.028	2.106 ± 0.022	2.120 ± 0.020
Relative	4.35 ± 0.08	4.29 ± 0.05	4.23 ± 0.07	4.32 ± 0.09
L. Kidney				
Absolute	1.704 ± 0.055	1.706 ± 0.063	1.842 ± 0.045	1.843 ± 0.044
Relative	3.57 ± 0.09	3.57 ± 0.09	3.70 ± 0.07	3.75 ± 0.04
R. Kidney				
Absolute	1.684 ± 0.047	1.727 ± 0.043	1.822 ± 0.034	1.769 ± 0.055
Relative	3.53 ± 0.08	3.62 ± 0.07	3.66 ± 0.06	3.59 ± 0.05
Liver				
Absolute	17.216 ± 0.534	16.803 ± 0.504	18.281 ± 0.566	18.506 ± 0.608
Relative	36.02 ± 0.76	35.16 ± 0.50	36.65 ± 0.80	37.57 ± 0.73
Female				
n	10	10	9	10
Necropsy body wt	289 ± 9	304 ± 5	302 ± 7	311 ± 7*
Brain				
Absolute	1.966 ± 0.014	1.909 ± 0.021	1.907 ± 0.029	1.917 ± 0.021
Relative	6.85 ± 0.20	6.30 ± 0.15*	6.33 ± 0.11*	6.19 ± 0.14**
L. Kidney				
Absolute	1.041 ± 0.018	1.069 ± 0.024	1.047 ± 0.033	1.051 ± 0.024
Relative	3.61 ± 0.08	3.52 ± 0.07	3.46 ± 0.06	3.38 ± 0.03*
R. Kidney				
Absolute	1.053 ± 0.025	1.072 ± 0.025	1.042 ± 0.032	1.058 ± 0.020
Relative	3.65 ± 0.07	3.53 ± 0.07	3.45 ± 0.06*	3.41 ± 0.03**
Liver				
Absolute	9.318 ± 0.277	9.490 ± 0.185	9.762 ± 0.125	9.861 ± 0.183
Relative	32.27 ± 0.66	31.25 ± 0.61	32.44 ± 0.75	31.78 ± 0.48

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

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	25.6 ± 1.2	26.8 ± 0.7	26.0 ± 1.0	24.0 ± 0.7	24.4 ± 0.2	21.8 ± 0.7**
Brain						
Absolute	0.452 ± 0.005	0.460 ± 0.009	0.442 ± 0.014	0.416 ± 0.013	0.450 ± 0.004	0.436 ± 0.006
Relative	17.80 ± 0.77	17.23 ± 0.67	17.16 ± 1.12	17.43 ± 0.94	18.45 ± 0.26	20.11 ± 0.84
Heart						
Absolute	0.132 ± 0.014	0.120 ± 0.004	0.125 ± 0.006[b]	0.120 ± 0.005	0.124 ± 0.004	0.102 ± 0.004**
Relative	5.13 ± 0.39	4.49 ± 0.19	4.95 ± 0.22[b]	4.99 ± 0.11	5.08 ± 0.17	4.68 ± 0.06
R. Kidney						
Absolute	0.208 ± 0.012	0.216 ± 0.002	0.224 ± 0.014	0.220 ± 0.007	0.218 ± 0.004	0.194 ± 0.009
Relative	8.11 ± 0.17	8.08 ± 0.22	8.61 ± 0.40	9.17 ± 0.14*	8.93 ± 0.10*	8.90 ± 0.27*
Liver						
Absolute	1.154 ± 0.107	1.222 ± 0.082	1.346 ± 0.081	1.226 ± 0.086	1.206 ± 0.022	0.920 ± 0.038*
Relative	44.75 ± 2.21	45.55 ± 2.62	51.61 ± 1.60	50.96 ± 2.64	49.43 ± 0.82	42.17 ± 0.47
Lungs						
Absolute	0.152 ± 0.011	0.160 ± 0.003	0.176 ± 0.009	0.192 ± 0.009*	0.204 ± 0.014*	0.158 ± 0.007*
Relative	5.98 ± 0.47	5.98 ± 0.15	6.81 ± 0.45	8.01 ± 0.33**	8.35 ± 0.52**	7.27 ± 0.36**
L. Testis						
Absolute	0.100 ± 0.003	0.101 ± 0.005	0.099 ± 0.003	0.095 ± 0.010	0.100 ± 0.011	0.101 ± 0.004
Relative	3.92 ± 0.17	3.77 ± 0.11	3.81 ± 0.16	3.94 ± 0.36	4.12 ± 0.45	4.64 ± 0.25
Thymus						
Absolute	0.041 ± 0.002	0.040 ± 0.003	0.043 ± 0.006	0.030 ± 0.003	0.059 ± 0.004*	0.032 ± 0.007
Relative	1.59 ± 0.04	1.50 ± 0.10	1.66 ± 0.27	1.28 ± 0.17	2.43 ± 0.17*	1.48 ± 0.32
Female						
n	5	5	5	5	4	5
Necropsy body wt	21.0 ± 1.0	18.0 ± 0.3*	18.8 ± 1.3*	16.8 ± 0.6**	17.0 ± 0.4**	15.2 ± 0.5**
Brain						
Absolute	0.440 ± 0.013	0.454 ± 0.005	0.430 ± 0.008	0.440 ± 0.015	0.453 ± 0.010	0.416 ± 0.017
Relative	21.03 ± 0.52	25.25 ± 0.52**	23.23 ± 1.35**	26.20 ± 0.40**	26.62 ± 0.10**	27.36 ± 0.71**
Heart						
Absolute	0.094 ± 0.004	0.096 ± 0.005	0.090 ± 0.000	0.100 ± 0.006	0.098 ± 0.005	0.082 ± 0.004
Relative	4.48 ± 0.08	5.33 ± 0.27	4.87 ± 0.29	5.94 ± 0.23**	5.73 ± 0.18**	5.39 ± 0.16**
R. Kidney						
Absolute	0.148 ± 0.008	0.148 ± 0.011	0.136 ± 0.006	0.152 ± 0.010	0.150 ± 0.006	0.126 ± 0.005
Relative	7.04 ± 0.16	8.24 ± 0.65	7.36 ± 0.54	9.01 ± 0.32**	8.82 ± 0.24*	8.29 ± 0.17**
Liver						
Absolute	0.964 ± 0.052	0.866 ± 0.033	0.784 ± 0.032	0.916 ± 0.039	0.870 ± 0.033	0.716 ± 0.089**
Relative	45.84 ± 0.57	48.05 ± 1.13	42.62 ± 3.53	54.59 ± 1.76	51.16 ± 1.22	47.24 ± 6.01
Lungs						
Absolute	0.150 ± 0.015	0.160 ± 0.007	0.144 ± 0.009	0.152 ± 0.006	0.175 ± 0.013	0.132 ± 0.006
Relative	7.12 ± 0.60	8.88 ± 0.31	7.78 ± 0.66	9.05 ± 0.14*	10.30 ± 0.77**	8.69 ± 0.29**
Thymus						
Absolute	0.056 ± 0.002	0.058 ± 0.003	0.057 ± 0.008	0.049 ± 0.003	0.059 ± 0.005	0.042 ± 0.003*
Relative	2.69 ± 0.15	3.19 ± 0.10	3.10 ± 0.52	2.94 ± 0.13	3.50 ± 0.35	2.82 ± 0.24

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

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	9	10	10	10	10	10
Necropsy body wt	32.8 ± 0.5	32.3 ± 0.5	29.9 ± 0.5	31.6 ± 0.8	32.1 ± 0.4	29.8 ± 0.7**
Brain						
Absolute	0.453 ± 0.004	0.434 ± 0.009	0.440 ± 0.009	0.427 ± 0.020	0.453 ± 0.004	0.424 ± 0.006
Relative	13.85 ± 0.22	13.48 ± 0.42	14.76 ± 0.42	13.64 ± 0.82	14.13 ± 0.17	14.31 ± 0.41
Heart						
Absolute	0.146 ± 0.004	0.134 ± 0.003	0.139 ± 0.003	0.132 ± 0.004*	0.135 ± 0.004*	0.115 ± 0.004**
Relative	4.44 ± 0.10	4.15 ± 0.10	4.66 ± 0.13	4.23 ± 0.25	4.20 ± 0.08	3.89 ± 0.20*
R. Kidney						
Absolute	0.268 ± 0.008	0.267 ± 0.006	0.263 ± 0.008	0.255 ± 0.008	0.272 ± 0.008	0.222 ± 0.006**
Relative	8.16 ± 0.16	8.28 ± 0.22	8.80 ± 0.21	8.17 ± 0.49	8.47 ± 0.20	7.46 ± 0.17
Liver						
Absolute	1.528 ± 0.097	1.452 ± 0.082	1.202 ± 0.032*	1.338 ± 0.076*	1.401 ± 0.076*	1.063 ± 0.045**
Relative	46.51 ± 2.69	44.78 ± 2.06	40.27 ± 1.18	42.76 ± 3.10	43.55 ± 2.10	35.54 ± 0.72**
Lungs						
Absolute	0.160 ± 0.006	0.169 ± 0.005	0.188 ± 0.006**	0.162 ± 0.005[b]	0.169 ± 0.007	0.147 ± 0.006[b]
Relative	4.88 ± 0.17	5.26 ± 0.23	6.29 ± 0.18**	5.22 ± 0.32[b]	5.28 ± 0.24	4.90 ± 0.19[b]
L. Testis						
Absolute	0.109 ± 0.002	0.107 ± 0.003[b]	0.111 ± 0.002	0.107 ± 0.001	0.117 ± 0.003	0.094 ± 0.003**
Relative	3.32 ± 0.07	3.32 ± 0.15[b]	3.74 ± 0.11	3.41 ± 0.14	3.67 ± 0.14	3.19 ± 0.15
Thymus						
Absolute	0.034 ± 0.004	0.035 ± 0.002	0.039 ± 0.003	0.034 ± 0.003	0.039 ± 0.002	0.031 ± 0.003
Relative	1.04 ± 0.11	1.09 ± 0.07	1.29 ± 0.10	1.08 ± 0.10	1.22 ± 0.06	1.04 ± 0.11
Female						
n	10	9	10	10	10	10
Necropsy body wt	24.8 ± 0.4	25.8 ± 0.7	24.9 ± 0.3	26.4 ± 0.7	25.3 ± 0.5	24.7 ± 0.6
Brain						
Absolute	0.452 ± 0.010	0.456 ± 0.005	0.454 ± 0.014	0.473 ± 0.006	0.451 ± 0.006	0.438 ± 0.005
Relative	18.29 ± 0.55	17.61 ± 0.43	18.28 ± 0.65	18.03 ± 0.56	17.88 ± 0.40	17.80 ± 0.34
Heart						
Absolute	0.110 ± 0.003	0.109 ± 0.005	0.108 ± 0.002[b]	0.120 ± 0.003	0.115 ± 0.003	0.106 ± 0.006
Relative	4.44 ± 0.13	4.18 ± 0.11	4.31 ± 0.06[b]	4.56 ± 0.11	4.55 ± 0.10	4.31 ± 0.24
R. Kidney						
Absolute	0.169 ± 0.003	0.169 ± 0.005	0.172 ± 0.003	0.188 ± 0.004	0.182 ± 0.006	0.173 ± 0.003
Relative	6.82 ± 0.07	6.50 ± 0.13	6.91 ± 0.11	7.17 ± 0.26	7.20 ± 0.21	7.03 ± 0.16
Liver						
Absolute	1.041 ± 0.036	1.153 ± 0.082[c]	0.992 ± 0.025	1.220 ± 0.075	1.056 ± 0.038	0.959 ± 0.051
Relative	41.95 ± 1.16	44.21 ± 1.84[c]	39.82 ± 0.80	45.89 ± 1.81	41.65 ± 0.94	38.64 ± 1.27
Lungs						
Absolute	0.157 ± 0.005	0.167 ± 0.017	0.157 ± 0.004	0.159 ± 0.008	0.153 ± 0.007	0.143 ± 0.003
Relative	6.34 ± 0.21	6.34 ± 0.45	6.31 ± 0.19	6.07 ± 0.37	6.05 ± 0.28	5.81 ± 0.16
Thymus						
Absolute	0.033 ± 0.003	0.040 ± 0.002	0.043 ± 0.004*	0.047 ± 0.001**[b]	0.044 ± 0.003**[b]	0.047 ± 0.002**
Relative	1.34 ± 0.12	1.55 ± 0.05	1.74 ± 0.18*	1.80 ± 0.05*[b]	1.76 ± 0.13*[b]	1.90 ± 0.07**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9
[c] n=8

TABLE F7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	46.7 ± 1.3	45.4 ± 1.5	46.1 ± 1.3	42.2 ± 1.3*
Brain				
Absolute	0.469 ± 0.004	0.462 ± 0.003	0.451 ± 0.006[b]	0.457 ± 0.007
Relative	10.11 ± 0.26	10.28 ± 0.33	9.72 ± 0.28[b]	10.92 ± 0.36
L. Kidney				
Absolute	0.355 ± 0.016	0.347 ± 0.017	0.338 ± 0.010	0.334 ± 0.010
Relative	7.60 ± 0.23	7.63 ± 0.18	7.35 ± 0.22	7.93 ± 0.18
R. Kidney				
Absolute	0.366 ± 0.012	0.360 ± 0.016	0.356 ± 0.009	0.359 ± 0.013
Relative	7.85 ± 0.15	7.92 ± 0.18	7.76 ± 0.21	8.54 ± 0.25
Liver				
Absolute	2.176 ± 0.126	2.036 ± 0.100	2.039 ± 0.155	1.801 ± 0.084*
Relative	46.28 ± 1.60	44.72 ± 1.12	43.89 ± 2.17	42.56 ± 0.81
Female				
n	11	10	10	10
Necropsy body wt	43.5 ± 1.1	38.4 ± 1.0**	41.0 ± 0.7**	38.1 ± 0.7**
Brain				
Absolute	0.483 ± 0.005	0.491 ± 0.009	0.476 ± 0.007	0.468 ± 0.003
Relative	11.16 ± 0.25	12.93 ± 0.65*	11.62 ± 0.21*	12.34 ± 0.24*
L. Kidney				
Absolute	0.214 ± 0.005	0.210 ± 0.005	0.211 ± 0.005	0.214 ± 0.007
Relative	4.93 ± 0.07	5.52 ± 0.23	5.15 ± 0.12	5.61 ± 0.17**
R. Kidney				
Absolute	0.233 ± 0.005	0.223 ± 0.005	0.222 ± 0.005	0.221 ± 0.005
Relative	5.37 ± 0.13	5.85 ± 0.25	5.40 ± 0.07	5.81 ± 0.13
Liver				
Absolute	1.691 ± 0.053	1.577 ± 0.028	1.558 ± 0.033*	1.508 ± 0.042**
Relative	38.87 ± 0.79	41.31 ± 1.39	38.01 ± 0.76	39.59 ± 0.77

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

TABLE F8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	10	9	10
Necropsy body wt	45.9 ± 1.3	46.4 ± 0.9	47.8 ± 1.2	45.7 ± 0.9
Brain				
Absolute	0.460 ± 0.007	0.477 ± 0.006	0.472 ± 0.007	0.501 ± 0.040
Relative	10.12 ± 0.43	10.33 ± 0.25	9.91 ± 0.24	10.95 ± 0.75
L. Kidney				
Absolute	0.381 ± 0.007	0.388 ± 0.012	0.396 ± 0.015	0.421 ± 0.042
Relative	8.34 ± 0.17	8.36 ± 0.19	8.29 ± 0.25	9.16 ± 0.77
R. Kidney				
Absolute	0.410 ± 0.010	0.404 ± 0.014	0.408 ± 0.014	0.449 ± 0.046
Relative	8.96 ± 0.23	8.70 ± 0.25	8.55 ± 0.24	9.75 ± 0.84
Liver				
Absolute	1.978 ± 0.084	1.982 ± 0.082	2.023 ± 0.117	2.063 ± 0.194
Relative	43.02 ± 1.14	42.60 ± 1.13	42.13 ± 1.64	44.92 ± 3.66
Female				
n	9	10	9	9
Necropsy body wt	45.3 ± 1.7	48.2 ± 1.8	47.8 ± 1.7	44.2 ± 0.9
Brain				
Absolute	0.494 ± 0.008	0.487 ± 0.007	0.489 ± 0.009	0.483 ± 0.008
Relative	10.99 ± 0.36	10.25 ± 0.47	10.34 ± 0.43	10.97 ± 0.36
L. Kidney				
Absolute	0.234 ± 0.006	0.257 ± 0.006*	0.244 ± 0.007	0.250 ± 0.008
Relative	5.18 ± 0.12	5.39 ± 0.19	5.13 ± 0.16	5.67 ± 0.20
R. Kidney				
Absolute	0.243 ± 0.009	0.266 ± 0.007	0.258 ± 0.007	0.261 ± 0.007
Relative	5.39 ± 0.17	5.57 ± 0.22	5.41 ± 0.14	5.93 ± 0.19
Liver				
Absolute	1.731 ± 0.048	1.874 ± 0.044	1.753 ± 0.055	1.689 ± 0.035
Relative	38.39 ± 0.89	39.14 ± 1.10	36.71 ± 0.63	38.27 ± 0.92

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

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology Data for Rats in the 14-Day Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	5	5	5	5	5	5
Hematocrit (%)	43.8 ± 1.0	42.6 ± 1.2	42.9 ± 0.6	44.3 ± 1.0	40.3 ± 1.4	41.6 ± 1.0
Hemoglobin (g/dL)	15.3 ± 0.3	15.9 ± 0.2	15.7 ± 0.3	15.9 ± 0.3	14.9 ± 0.3	14.8 ± 0.3
Erythrocytes (10^6/µL)	8.10 ± 0.21	7.80 ± 0.25	7.96 ± 0.15	8.04 ± 0.08	7.54 ± 0.26	7.97 ± 0.19
Mean cell volume (fL)	53.0 ± 0.3	53.6 ± 0.6	52.8 ± 0.4	53.8 ± 0.9	52.4 ± 0.4	51.2 ± 0.2*
Leukocytes (10^3/µL)	2.58 ± 0.36	3.38 ± 0.24	3.84 ± 0.37*	3.60 ± 0.26*	3.58 ± 0.22*	6.32 ± 0.82**
Segmented neutrophils (10^3/µL)	0.76 ± 0.11	1.03 ± 0.11	0.90 ± 0.19	0.93 ± 0.10	0.92 ± 0.12	3.52 ± 0.28**
Lymphocytes (10^3/µL)	1.70 ± 0.36	2.24 ± 0.22	2.77 ± 0.24	2.53 ± 0.18	2.26 ± 0.16	2.46 ± 0.62
Monocytes (10^3/µL)	0.10 ± 0.03	0.07 ± 0.03	0.12 ± 0.03	0.10 ± 0.03	0.38 ± 0.11	0.33 ± 0.09*
Eosinophils (10^3/µL)	0.02 ± 0.01	0.04 ± 0.02	0.05 ± 0.03	0.04 ± 0.02	0.02 ± 0.01	0.01 ± 0.01
Female						
n	5	5	5	5	5	5
Hematocrit (%)	42.9 ± 1.4	43.6 ± 0.5	45.1 ± 0.5	43.4 ± 0.7	43.9 ± 0.8	39.3 ± 1.1
Hemoglobin (g/dL)	15.3 ± 0.3	16.0 ± 0.2	16.3 ± 0.1	16.0 ± 0.3	15.7 ± 0.2	14.0 ± 0.4
Erythrocytes (10^6/µL)	7.87 ± 0.16	8.10 ± 0.09	8.28 ± 0.08	8.03 ± 0.11	7.88 ± 0.02	7.42 ± 0.22
Mean cell volume (fL)	53.4 ± 0.7	52.6 ± 0.4	53.6 ± 0.2	52.8 ± 0.4	54.6 ± 0.9	51.8 ± 0.4
Leukocytes (10^3/µL)	2.72 ± 0.26	3.38 ± 0.09	3.22 ± 0.41	3.00 ± 0.64	2.72 ± 0.25	4.26 ± 0.32*
Segmented neutrophils (10^3/µL)	0.55 ± 0.07	0.75 ± 0.06	0.86 ± 0.23	0.68 ± 0.25	0.55 ± 0.12	1.62 ± 0.23*
Lymphocytes (10^3/µL)	2.02 ± 0.18	2.35 ± 0.10	2.08 ± 0.23	2.05 ± 0.37	1.95 ± 0.25	2.23 ± 0.23
Monocytes (10^3/µL)	0.07 ± 0.02	0.25 ± 0.04**	0.25 ± 0.13*	0.20 ± 0.04*	0.18 ± 0.05*	0.34 ± 0.14**
Eosinophils (10^3/µL)	0.08 ± 0.04	0.04 ± 0.01	0.02 ± 0.01	0.07 ± 0.04	0.04 ± 0.02	0.07 ± 0.03

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error

TABLE G2
Hematology Data for Rats in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,600 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm
Male						
n	10	10	10	10	10	10
Hematocrit (%)	40.8 ± 1.2	42.3 ± 0.9	42.2 ± 1.0	44.1 ± 0.6*	45.2 ± 1.4*	45.8 ± 1.5*
Hemoglobin (g/dL)	15.4 ± 0.3	15.4 ± 0.2	15.8 ± 0.3	16.0 ± 0.2	16.0 ± 0.3	15.7 ± 0.4
Erythrocytes (10^6/µL)	7.87 ± 0.15	8.20 ± 0.18	8.13 ± 0.17	8.60 ± 0.08**	8.33 ± 0.13**	8.82 ± 0.19**
Mean cell volume (fL)	52.7 ± 0.6	51.9 ± 0.5	52.1 ± 0.4	51.4 ± 0.4	54.2 ± 0.9	52.2 ± 0.8
Leukocytes (10^3/µL)	3.17 ± 0.17	3.32 ± 0.14	3.27 ± 0.17	3.18 ± 0.09	3.94 ± 0.19*	3.07 ± 0.18
Segmented neutrophils (10^3/µL)	0.61 ± 0.06	1.19 ± 0.06**	1.15 ± 0.12**	1.29 ± 0.10**	1.73 ± 0.12**	1.30 ± 0.08**
Lymphocytes (10^3/µL)	2.51 ± 0.19	2.08 ± 0.12	2.05 ± 0.12	1.80 ± 0.10**	2.17 ± 0.15*	1.73 ± 0.17**
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.02	0.01 ± 0.00
Eosinophils (10^3/µL)	0.04 ± 0.02	0.05 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.05 ± 0.02	0.04 ± 0.01
Female						
n	10	10	10	10	10	10
Hematocrit (%)	42.0 ± 0.8	40.4 ± 0.7	41.3 ± 0.8	41.1 ± 0.8	42.3 ± 0.8	43.1 ± 1.1
Hemoglobin (g/dL)	15.7 ± 0.2	15.5 ± 0.2	15.1 ± 0.2	15.5 ± 0.3	15.6 ± 0.3	16.1 ± 0.3
Erythrocytes (10^6/µL)	7.34 ± 0.13	7.09 ± 0.15	7.39 ± 0.16	7.16 ± 0.16	7.59 ± 0.15	7.91 ± 0.16*
Mean cell volume (fL)	57.3 ± 0.7	57.0 ± 0.7	56.0 ± 0.5	56.5 ± 0.8	56.0 ± 0.6	54.6 ± 0.5**
Leukocytes (10^3/µL)	3.79 ± 0.33	2.98 ± 0.09*	3.09 ± 0.16	2.78 ± 0.09**	2.75 ± 0.13**	2.78 ± 0.21**
Segmented neutrophils (10^3/µL)	1.05 ± 0.17	0.72 ± 0.08	0.76 ± 0.09	0.58 ± 0.06**	0.73 ± 0.08	0.87 ± 0.11
Lymphocytes (10^3/µL)	2.70 ± 0.23	2.23 ± 0.08	2.26 ± 0.13	2.12 ± 0.09*	1.95 ± 0.12**	1.82 ± 0.12**
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/µL)	0.04 ± 0.01	0.03 ± 0.01	0.07 ± 0.02	0.06 ± 0.02	0.07 ± 0.01	0.09 ± 0.02*

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	8	9	10	10
Hematology				
Hematocrit (%)	48.6 ± 0.8	48.2 ± 0.9	46.1 ± 0.8	49.8 ± 1.0
Hemoglobin (g/dL)	15.2 ± 0.2	15.4 ± 0.1	14.4 ± 0.2	15.4 ± 0.3
Erythrocytes (10^6/µL)	10.09 ± 0.16	10.05 ± 0.17	9.62 ± 0.13	10.20 ± 0.22
Mean cell volume (fL)	48.4 ± 0.3	48.1 ± 0.3	47.8 ± 0.5	48.8 ± 0.3
Mean cell hemoglobin (pg)	15.1 ± 0.1	15.3 ± 0.2	15.0 ± 0.1	15.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.4 ± 0.2	31.9 ± 0.5	31.3 ± 0.3	30.9 ± 0.2
Platelets (10^3/µL)	697 ± 11	659 ± 66	648 ± 65	678 ± 66
Reticulocytes (10^6/µL)	0.17 ± 0.02	0.16 ± 0.02	0.16 ± 0.01	0.14 ± 0.02
Leukocytes (10^3/µL)	8.75 ± 0.54	8.09 ± 0.34	7.76 ± 0.51	8.16 ± 0.39
Segmented neutrophils (10^3/µL)	1.83 ± 0.21	1.78 ± 0.15	1.83 ± 0.30	1.70 ± 0.16
Lymphocytes (10^3/µL)	6.76 ± 0.46	6.21 ± 0.34	5.83 ± 0.40	6.36 ± 0.35
Monocytes (10^3/µL)	0.04 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01
Eosinophils (10^3/µL)	0.14 ± 0.04	0.12 ± 0.03	0.09 ± 0.03	0.08 ± 0.04
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
n	8	10	10	10
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	19.4 ± 0.7	18.3 ± 0.7	16.5 ± 0.8*	18.1 ± 0.9
Creatinine (mg/dL)	0.55 ± 0.02	0.56 ± 0.04	0.59 ± 0.06	0.56 ± 0.03
Alanine aminotransferase (IU/L)	79 ± 8	76 ± 9	78 ± 10	73 ± 8
Aspartate aminotransferase (IU/L)	105 ± 8	98 ± 7	100 ± 8	100 ± 9
Sorbitol dehydrogenase (IU/L)	54 ± 8	49 ± 7	47 ± 6	41 ± 4
Female				
n	8	10	10	10
Hematology				
Hematocrit (%)	48.0 ± 0.5	47.7 ± 0.7	48.3 ± 0.9	48.5 ± 0.4
Hemoglobin (g/dL)	15.3 ± 0.2	15.3 ± 0.1	15.3 ± 0.2	15.3 ± 0.1
Erythrocytes (10^6/µL)	9.22 ± 0.07	9.18 ± 0.10	9.24 ± 0.16	9.44 ± 0.08
Mean cell volume (fL)	52.1 ± 0.5	52.0 ± 0.4	52.0 ± 0.3	51.5 ± 0.4
Mean cell hemoglobin (pg)	16.6 ± 0.1	16.6 ± 0.1	16.6 ± 0.2	16.2 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	31.7 ± 0.4	32.0 ± 0.3	31.9 ± 0.6	31.6 ± 0.2
Platelets (10^3/µL)	633 ± 24	632 ± 29	519 ± 58	615 ± 63
Reticulocytes (10^6/µL)	0.13 ± 0.01	0.15 ± 0.01	0.14 ± 0.02	0.15 ± 0.01
Leukocytes (10^3/µL)	3.91 ± 0.35	4.42 ± 0.34	3.55 ± 0.27	5.37 ± 0.65
Segmented neutrophils (10^3/µL)	0.91 ± 0.14	1.04 ± 0.11	0.87 ± 0.14	1.17 ± 0.15
Lymphocytes (10^3/µL)	2.93 ± 0.27	3.31 ± 0.25	2.64 ± 0.18	4.18 ± 0.51
Monocytes (10^3/µL)	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
n	10	10	10	10
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	18.5 ± 0.5	17.9 ± 1.1	17.7 ± 0.7	16.4 ± 1.2
Creatinine (mg/dL)	0.55 ± 0.03	0.56 ± 0.04	0.55 ± 0.04	0.55 ± 0.02
Alanine aminotransferase (IU/L)	43 ± 3	34 ± 2	38 ± 3	38 ± 3
Aspartate aminotransferase (IU/L)	96 ± 6	75 ± 6	91 ± 4	83 ± 6
Sorbitol dehydrogenase (IU/L)	36 ± 3	25 ± 3*	29 ± 3	27 ± 3*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Female				
n	8	10	10	10
Hematology				
Hematocrit (%)	48.0 ± 0.5	47.7 ± 0.7	48.3 ± 0.9	48.5 ± 0.4
Hemoglobin (g/dL)	15.3 ± 0.2	15.3 ± 0.1	15.3 ± 0.2	15.3 ± 0.1
Erythrocytes (10^6/µL)	9.22 ± 0.07	9.18 ± 0.10	9.24 ± 0.16	9.44 ± 0.08
Mean cell volume (fL)	52.1 ± 0.5	52.0 ± 0.4	52.0 ± 0.3	51.5 ± 0.4
Mean cell hemoglobin (pg)	16.6 ± 0.1	16.6 ± 0.1	16.6 ± 0.2	16.2 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	31.7 ± 0.4	32.0 ± 0.3	31.9 ± 0.6	31.6 ± 0.2
Platelets (10^3/µL)	633 ± 24	632 ± 29	519 ± 58	615 ± 63
Reticulocytes (10^6/µL)	0.13 ± 0.01	0.15 ± 0.01	0.14 ± 0.02	0.15 ± 0.01
Leukocytes (10^3/µL)	3.91 ± 0.35	4.42 ± 0.34	3.55 ± 0.27	5.37 ± 0.65
Segmented neutrophils (10^3/µL)	0.91 ± 0.14	1.04 ± 0.11	0.87 ± 0.14	1.17 ± 0.15
Lymphocytes (10^3/µL)	2.93 ± 0.27	3.31 ± 0.25	2.64 ± 0.18	4.18 ± 0.51
Monocytes (10^3/µL)	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/µL)	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.06 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
n	10	10	10	10
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	18.5 ± 0.5	17.9 ± 1.1	17.7 ± 0.7	16.4 ± 1.2
Creatinine (mg/dL)	0.55 ± 0.03	0.56 ± 0.04	0.55 ± 0.04	0.55 ± 0.02
Alanine aminotransferase (IU/L)	43 ± 3	34 ± 2	38 ± 3	38 ± 3
Aspartate aminotransferase (IU/L)	96 ± 6	75 ± 6	91 ± 4	83 ± 6
Sorbitol dehydrogenase (IU/L)	36 ± 3	25 ± 3*	29 ± 3	27 ± 3*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error

TABLE G4
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	9	9	7
Hematology				
Hematocrit (%)	52.1 ± 1.1	50.8 ± 2.0	50.7 ± 1.2	52.9 ± 0.6
Hemoglobin (g/dL)	14.6 ± 0.2	14.5 ± 0.4	14.4 ± 0.3	14.7 ± 0.1
Erythrocytes (10^6/µL)	9.79 ± 0.15	9.45 ± 0.35	9.62 ± 0.19	9.91 ± 0.11
Mean cell volume (fL)	53.2 ± 0.6	53.6 ± 0.6	52.4 ± 0.7	53.1 ± 0.3
Mean cell hemoglobin (pg)	14.9 ± 0.2	15.4 ± 0.3	15.0 ± 0.4	14.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	28.0 ± 0.3	28.7 ± 0.6	28.6 ± 0.5	28.0 ± 0.2
Platelets (10^3/µL)	744 ± 51	812 ± 39	669 ± 65	808 ± 21
Reticulocytes (10^6/µL)	0.16 ± 0.02	0.18 ± 0.02	0.20 ± 0.02	0.20 ± 0.03
Leukocytes (10^3/µL)	8.62 ± 0.65	8.07 ± 0.67	7.41 ± 0.35	9.50 ± 0.95
Segmented neutrophils (10^3/µL)	2.65 ± 0.44	2.19 ± 0.28	2.07 ± 0.08	3.35 ± 0.73
Lymphocytes (10^3/µL)	5.80 ± 0.53	5.68 ± 0.54	5.15 ± 0.38	5.87 ± 0.37
Monocytes (10^3/µL)	0.08 ± 0.03	0.05 ± 0.03	0.04 ± 0.02	0.18 ± 0.08
Eosinophils (10^3/µL)	0.09 ± 0.03	0.15 ± 0.05	0.14 ± 0.02	0.10 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.02 ± 0.02	0.04 ± 0.02	0.01 ± 0.01	0.02 ± 0.02
n	10	9	9	8
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	13.5 ± 1.1	17.2 ± 0.8	15.8 ± 1.2	13.8 ± 1.4
Creatinine (mg/dL)	0.49 ± 0.02	0.51 ± 0.04	0.52 ± 0.03	0.48 ± 0.03
Alanine aminotransferase (IU/L)	61 ± 5	59 ± 13	63 ± 6	67 ± 13
Aspartate aminotransferase (IU/L)	71 ± 5	68 ± 9	75 ± 6	74 ± 9
Sorbitol dehydrogenase (IU/L)	38 ± 5	37 ± 8	40 ± 4	38 ± 9

TABLE G4
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Female				
n	8	9	9	8
Hematology				
Hematocrit (%)	50.6 ± 0.6	49.7 ± 1.1	50.9 ± 0.6	51.8 ± 0.6
Hemoglobin (g/dL)	14.9 ± 0.1	14.6 ± 0.3	14.7 ± 0.2	14.7 ± 0.1
Erythrocytes (10^6/µL)	9.03 ± 0.06	8.85 ± 0.16	9.05 ± 0.10	9.13 ± 0.14
Mean cell volume (fL)	56.0 ± 0.7	55.9 ± 0.5	56.0 ± 0.4	56.8 ± 0.6
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.5 ± 0.1	16.2 ± 0.1**	16.1 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	29.5 ± 0.4	29.5 ± 0.3	28.9 ± 0.2	28.4 ± 0.2*
Platelets (10^3/µL)	627 ± 31	597 ± 67	628 ± 42	659 ± 27
Reticulocytes (10^6/µL)	0.16 ± 0.02	0.14 ± 0.02[b]	0.18 ± 0.01	0.15 ± 0.02
Leukocytes (10^3/µL)	4.01 ± 0.51	4.04 ± 0.25	5.72 ± 0.77	4.63 ± 0.58
Segmented neutrophils (10^3/µL)	0.88 ± 0.08	1.01 ± 0.12[b]	1.62 ± 0.21*	1.24 ± 0.23
Lymphocytes (10^3/µL)	3.07 ± 0.48	2.96 ± 0.28[b]	4.00 ± 0.61	3.30 ± 0.37
Monocytes (10^3/µL)	0.01 ± 0.01	0.03 ± 0.01[b]	0.03 ± 0.01	0.04 ± 0.02
Eosinophils (10^3/µL)	0.05 ± 0.02	0.05 ± 0.02[b]	0.07 ± 0.02	0.05 ± 0.02
Nucleated erythrocytes (10^3/µL)	0.02 ± 0.01	0.01 ± 0.01[b]	0.02 ± 0.01	0.02 ± 0.01
n	10	10	9	10
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	13.9 ± 1.0	15.7 ± 0.9	14.3 ± 0.8	13.5 ± 1.1
Creatinine (mg/dL)	0.44 ± 0.03	0.41 ± 0.02	0.47 ± 0.04	0.43 ± 0.02
Alanine aminotransferase (IU/L)	37 ± 2	39 ± 2	38 ± 3	35 ± 3
Aspartate aminotransferase (IU/L)	54 ± 4	52 ± 8	67 ± 15	53 ± 4
Sorbitol dehydrogenase (IU/L)	25 ± 1	31 ± 2*	43 ± 13	28 ± 1

* 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=8

TABLE G5
Hematology Data for Mice in the 14-Day Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	3	5	5	5	5	5
Hematocrit (%)	45.5 ± 3.9	49.3 ± 3.1	46.3 ± 3.0	46.9 ± 1.1	46.9 ± 0.9	46.6 ± 1.0
Hemoglobin (g/dL)	15.0 ± 0.4	14.9 ± 0.5	14.5 ± 0.9	15.1 ± 0.5	14.9 ± 0.3	14.8 ± 0.5
Erythrocytes (10^6/µL)	9.08 ± 0.39	9.18 ± 0.37	8.82 ± 0.58	8.98 ± 0.15	9.18 ± 0.18	9.04 ± 0.25
Mean cell volume (fL)	50.7 ± 2.3	53.8 ± 1.1	52.8 ± 0.2	52.4 ± 0.5	51.6 ± 0.5	51.8 ± 1.1
Leukocytes (10^3/µL)	2.30 ± 0.23	3.96 ± 0.33	3.94 ± 0.50	5.18 ± 2.23	2.58 ± 0.44	3.54 ± 1.20
Segmented neutrophils (10^3/µL)	0.84 ± 0.23	1.61 ± 0.25	1.53 ± 0.60	2.65 ± 1.47	0.74 ± 0.17	0.83 ± 0.11
Lymphocytes (10^3/µL)	1.35 ± 0.08	2.10 ± 0.30	2.18 ± 0.29	2.26 ± 0.70	1.59 ± 0.26	2.49 ± 1.11
Monocytes (10^3/µL)	0.08 ± 0.02	0.22 ± 0.07	0.22 ± 0.07	0.26 ± 0.10	0.21 ± 0.04	0.21 ± 0.07
Eosinophils (10^3/µL)	0.03 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.01 ± 0.01
Female						
n	4	5	4	5	3	5
Hematocrit (%)	43.6 ± 1.3	47.6 ± 0.8	51.2 ± 1.1**	47.8 ± 0.4	44.5 ± 2.5	42.5 ± 2.9
Hemoglobin (g/dL)	14.0 ± 0.3	15.2 ± 0.2	16.2 ± 0.3**	15.1 ± 0.1	14.7 ± 0.6	13.7 ± 1.0
Erythrocytes (10^6/µL)	8.41 ± 0.19	9.15 ± 0.16	9.75 ± 0.20**	9.11 ± 0.06	8.97 ± 0.43	8.46 ± 0.52
Mean cell volume (fL)	52.0 ± 1.2	52.2 ± 0.2	53.0 ± 0.7	52.6 ± 0.2	50.0 ± 1.5	50.4 ± 0.5
Leukocytes (10^3/µL)	1.83 ± 0.24	1.76 ± 0.09	3.20 ± 0.60	2.66 ± 0.18	2.67 ± 0.29	5.74 ± 4.14
Segmented neutrophils (10^3/µL)	0.35 ± 0.14[b]	0.59 ± 0.11	0.87 ± 0.18*	0.99 ± 0.14*	0.84 ± 0.14	3.84 ± 3.23
Lymphocytes (10^3/µL)	1.25 ± 0.14[b]	1.03 ± 0.10	2.23 ± 0.47	1.53 ± 0.12	1.67 ± 0.29	1.65 ± 0.70
Monocytes (10^3/µL)	0.06 ± 0.01[b]	0.11 ± 0.04	0.07 ± 0.03	0.12 ± 0.04	0.09 ± 0.03	0.21 ± 0.17
Eosinophils (10^3/µL)	0.03 ± 0.02[b]	0.02 ± 0.01	0.03 ± 0.03	0.01 ± 0.01	0.07 ± 0.02	0.22[c]

* 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=3
c n=1; no standard error calculated

TABLE G6
Hematology Data for Mice in the 13-Week Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	3,130 ppm	6,250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	9	10	10	10	10	10
Hematocrit (%)	46.1 ± 0.9	47.6 ± 1.1	52.6 ± 2.1	45.2 ± 1.0	45.6 ± 1.3	38.3 ± 1.5**
Hemoglobin (g/dL)	14.4 ± 0.2	15.2 ± 0.4	16.4 ± 0.5	14.5 ± 0.3	14.2 ± 0.4	12.1 ± 0.5*
Erythrocytes (10^6/µL)	8.77 ± 0.24	9.28 ± 0.18	10.06 ± 0.33*	9.02 ± 0.17	9.17 ± 0.24	8.71 ± 0.36
Mean cell volume (fL)	51.4 ± 0.4	51.3 ± 0.6	52.0 ± 0.6	50.3 ± 0.3	50.0 ± 0.6	43.6 ± 1.2**
Leukocytes (10^3/µL)	3.48 ± 0.13	2.52 ± 0.25*	3.28 ± 0.12	3.24 ± 0.43	2.40 ± 0.38**	2.85 ± 0.54**
Segmented neutrophils (10^3/µL)	1.52 ± 0.27	0.92 ± 0.16	1.12 ± 0.10	1.60 ± 0.27	0.81 ± 0.10	1.04 ± 0.22[b]
Lymphocytes (10^3/µL)	1.87 ± 0.21	1.49 ± 0.15	2.04 ± 0.13	1.55 ± 0.28	1.54 ± 0.32	1.87 ± 0.39[b]
Monocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01[b]
Eosinophils (10^3/µL)	0.08 ± 0.02	0.10 ± 0.03	0.10 ± 0.03	0.05 ± 0.02	0.05 ± 0.01	0.03 ± 0.01[b]
Female						
n	10	6	8	9	10	10
Hematocrit (%)	45.4 ± 1.7	50.1 ± 1.7	49.4 ± 1.6	47.9 ± 1.5	46.4 ± 1.2	40.7 ± 1.5
Hemoglobin (g/dL)	14.4 ± 0.5	15.3 ± 0.4	14.9 ± 0.4	14.4 ± 0.3	14.8 ± 0.4	12.8 ± 0.5*
Erythrocytes (10^6/µL)	8.54 ± 0.33	9.57 ± 0.22	8.87 ± 0.24	8.95 ± 0.19	8.89 ± 0.21	8.80 ± 0.35
Mean cell volume (fL)	52.4 ± 1.4	49.7 ± 3.2[c]	54.6 ± 1.9	52.6 ± 0.7	52.3 ± 0.2	46.5 ± 1.1**
Leukocytes (10^3/µL)	2.90 ± 0.44	2.78 ± 0.34	2.54 ± 0.39	2.19 ± 0.17	2.11 ± 0.21	2.46 ± 0.32
Segmented neutrophils (10^3/µL)	0.62 ± 0.13	1.07 ± 0.14	1.09 ± 0.22	0.78 ± 0.13	0.72 ± 0.14	0.88 ± 0.18
Lymphocytes (10^3/µL)	1.89 ± 0.44	1.65 ± 0.23	1.37 ± 0.17	1.37 ± 0.13	1.33 ± 0.18	1.55 ± 0.17
Monocytes (10^3/µL)	0.01 ± 0.01	0.03 ± 0.01	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/µL)	0.08 ± 0.02	0.03 ± 0.02	0.05 ± 0.03	0.04 ± 0.01	0.06 ± 0.01	0.03 ± 0.01

* 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

TABLE G7
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	9	9	10	9
Hematology				
Hematocrit (%)	50.3 ± 0.7	46.7 ± 2.0	49.3 ± 0.8	50.3 ± 0.7
Hemoglobin (g/dL)	16.3 ± 0.2	15.1 ± 0.8	16.0 ± 0.2	16.4 ± 0.3
Erythrocytes (10^6/µL)	10.41 ± 0.14	9.98 ± 0.40	10.42 ± 0.13	10.87 ± 0.17
Mean cell hemoglobin (pg)	15.7 ± 0.2	15.0 ± 0.2	15.4 ± 0.2	15.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.3	31.0 ± 1.4	32.5 ± 0.5	32.5 ± 0.4
Mean cell volume (fL)	48.3 ± 0.6	46.9 ± 0.5*	47.1 ± 0.3*	46.4 ± 0.3**
Platelets (10^3/µL)	1,084 ± 51	1,160 ± 73	1,094 ± 51	1,038 ± 44
Reticulocytes (10^6/µL)	0.17 ± 0.02	0.45 ± 0.31	0.19 ± 0.01	0.20 ± 0.03
Leukocytes (10^3/µL)	5.91 ± 0.42	6.38 ± 0.32	6.16 ± 0.64	5.80 ± 0.16
Segmented neutrophils (10^3/µL)	1.09 ± 0.16	1.32 ± 0.15	1.38 ± 0.36	1.09 ± 0.15
Lymphocytes (10^3/µL)	4.26 ± 0.53	4.84 ± 0.25	4.61 ± 0.42	4.58 ± 0.19
Monocytes (10^3/µL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Eosinophils (10^3/µL)	0.18 ± 0.05	0.21 ± 0.05	0.17 ± 0.03	0.11 ± 0.03
n	10	10	10	9
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	28.9 ± 3.3	31.4 ± 2.0	31.6 ± 2.2	34.4 ± 1.1
Creatinine (mg/dL)	0.25 ± 0.03	0.33 ± 0.03	0.32 ± 0.03	0.30 ± 0.02
Alanine aminotransferase (IU/L)	40 ± 3	37 ± 6	43 ± 5	45 ± 5
Aspartate aminotransferase (IU/L)	114 ± 17	103 ± 11	110 ± 17	201 ± 70
Sorbitol dehydrogenase (IU/L)	54 ± 5	57 ± 8	53 ± 3	60 ± 5
Female				
n	11	10	10	10
Hematology				
Hematocrit (%)	49.9 ± 0.4	49.4 ± 0.3	49.8 ± 0.5	48.9 ± 0.5
Hemoglobin (g/dL)	16.0 ± 0.1	15.8 ± 0.1	16.1 ± 0.1	15.8 ± 0.1
Erythrocytes (10^6/µL)	10.34 ± 0.09	10.18 ± 0.10	10.51 ± 0.07	10.15 ± 0.09
Mean cell hemoglobin (pg)	15.5 ± 0.2	15.6 ± 0.1	15.3 ± 0.1	15.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.3	32.0 ± 0.2	32.2 ± 0.3	32.3 ± 0.3
Mean cell volume (fL)	48.6 ± 0.4	48.8 ± 0.5	47.3 ± 0.4	48.3 ± 0.4
Platelets (10^3/µL)	1,015 ± 23	979 ± 61	955 ± 37	1,003 ± 35
Reticulocytes (10^6/µL)	0.14 ± 0.02	0.14 ± 0.01	0.17 ± 0.02	0.14 ± 0.01
Leukocytes (10^3/µL)	4.04 ± 0.20	3.82 ± 0.28	3.70 ± 0.24	3.80 ± 0.30
Segmented neutrophils (10^3/µL)	0.96 ± 0.25	0.53 ± 0.09	0.78 ± 0.07	0.80 ± 0.13
Lymphocytes (10^3/µL)	2.95 ± 0.33	3.17 ± 0.27	2.82 ± 0.22	2.90 ± 0.23
Eosinophils (10^3/µL)	0.10 ± 0.03	0.11 ± 0.03	0.10 ± 0.03	0.10 ± 0.03
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	27.3 ± 1.7	28.3 ± 1.3	29.5 ± 1.9	28.4 ± 2.2
Creatinine (mg/dL)	0.26 ± 0.02	0.62 ± 0.34	0.21 ± 0.04	0.31 ± 0.01
Alanine aminotransferase (IU/L)	23 ± 2	47 ± 20	24 ± 2	22 ± 1
Aspartate aminotransferase (IU/L)	92 ± 15	160 ± 49	104 ± 11	115 ± 20
Sorbitol dehydrogenase (IU/L)	39 ± 6	55 ± 13	41 ± 4	34 ± 3

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error

TABLE G8
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	10	9	10
Hematology				
Hematocrit (%)	47.2 ± 0.7	48.0 ± 0.6	47.0 ± 1.1	50.9 ± 1.4**
Hemoglobin (g/dL)	15.0 ± 0.2	15.3 ± 0.2	15.0 ± 0.3	16.1 ± 0.4**
Erythrocytes (10^6/µL)	10.34 ± 0.11	10.35 ± 0.18	10.26 ± 0.24	11.03 ± 0.33*
Mean cell volume (fL)	45.7 ± 0.4	46.2 ± 0.5	45.8 ± 0.4	46.0 ± 0.3
Mean cell hemoglobin (pg)	14.5 ± 0.1	14.8 ± 0.1	14.6 ± 0.1	14.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.8 ± 0.3	32.0 ± 0.3	31.9 ± 0.2	31.7 ± 0.2
Platelets (10^3/µL)	1,377 ± 68	1,360 ± 36	1,322 ± 59	1,337 ± 30
Reticulocytes (10^6/µL)	0.09 ± 0.02	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.03
Leukocytes (10^3/µL)	5.46 ± 0.38	4.94 ± 0.42	5.62 ± 0.75	5.42 ± 0.33
Segmented neutrophils (10^3/µL)	1.26 ± 0.16	1.08 ± 0.12	1.16 ± 0.19	1.40 ± 0.21
Lymphocytes (10^3/µL)	4.09 ± 0.33	3.73 ± 0.32	4.35 ± 0.66	3.92 ± 0.16
Eosinophils (10^3/µL)	0.11 ± 0.03	0.13 ± 0.02	0.11 ± 0.02	0.10 ± 0.02
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	34.0 ± 1.6	30.5 ± 1.9	31.8 ± 3.0	31.1 ± 1.7
Creatinine (mg/dL)	0.35 ± 0.02	0.35 ± 0.02	0.38 ± 0.04	0.36 ± 0.02
Alanine aminotransferase (IU/L)	35 ± 4	36 ± 5	39 ± 4	33 ± 3
Aspartate aminotransferase (IU/L)	71 ± 11	64 ± 10	89 ± 10	75 ± 10
Sorbitol dehydrogenase (IU/L)	69 ± 3	68 ± 6	72 ± 6	61 ± 7
Female				
n	9	10	9	9
Hematology				
Hematocrit (%)	47.9 ± 0.6	49.0 ± 0.5	49.1 ± 0.8	49.0 ± 0.5
Hemoglobin (g/dL)	15.3 ± 0.1	15.5 ± 0.2	15.3 ± 0.3	15.3 ± 0.1
Erythrocytes (10^6/µL)	10.25 ± 0.09	10.48 ± 0.10	10.44 ± 0.22	10.39 ± 0.11
Mean cell volume (fL)	46.8 ± 0.4	46.8 ± 0.4	47.1 ± 0.6	47.0 ± 0.2
Mean cell hemoglobin (pg)	14.9 ± 0.1	14.8 ± 0.1	14.7 ± 0.1	14.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	31.9 ± 0.4	31.8 ± 0.2	31.3 ± 0.3	31.4 ± 0.2
Platelets (10^3/µL)	1,158 ± 24	1,127 ± 24	1,089 ± 26	1,079 ± 43
Reticulocytes (10^6/µL)	0.10 ± 0.02	0.08 ± 0.01	0.15 ± 0.03	0.13 ± 0.02
Leukocytes (10^3/µL)	3.13 ± 0.36	3.60 ± 0.30	3.33 ± 0.23	3.11 ± 0.15
Segmented neutrophils (10^3/µL)	0.83 ± 0.06	0.80 ± 0.11	0.83 ± 0.08	0.86 ± 0.09
Lymphocytes (10^3/µL)	2.23 ± 0.33	2.72 ± 0.23	2.45 ± 0.19	2.18 ± 0.14
Eosinophils (10^3/µL)	0.08 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.07 ± 0.03
Nucleated erythrocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry				
Blood urea nitrogen (mg/dL)	25.1 ± 1.5	28.0 ± 1.7	24.3 ± 1.7	24.2 ± 0.9
Creatinine (mg/dL)	0.38 ± 0.03	0.34 ± 0.03	0.38 ± 0.06	0.38 ± 0.04
Alanine aminotransferase (IU/L)	22 ± 1	23 ± 1	25 ± 2	24 ± 1
Aspartate aminotransferase (IU/L)	63 ± 8	64 ± 12	86 ± 15	90 ± 15
Sorbitol dehydrogenase (IU/L)	47 ± 2	45 ± 3	41 ± 6	46 ± 3

* 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

APPENDIX H
TISSUE METAL CONCENTRATION ANALYSES

METHODOLOGY OF TISSUE METAL CONCENTRATION ANALYSES FOR RATS AND MICE

Tissue metal analyses were performed in conjunction with the 9- and 15-month interim evaluations. Brain, kidney, liver, and pancreas tissues were collected for testing from F344/N rats and B6C3F$_1$ mice; plasma was also collected from rats. Tests were performed to determine the concentration of iron, zinc, copper, and manganese in each tissue.

Inductively coupled argon plasma (ICAP) emission spectrometry, a simultaneous multi-element analytical method, was used at Battelle Columbus Laboratories to determine the concentration of the four metals in the tissues of interim evaluation animals.

Tissue samples were weighed and combined in a beaker with 2 mL of concentrated nitric acid (HNO_3) and 1 mL of perchloric acid ($HClO_4$). Tissue/acid mixtures were heated at low temperature to facilitate tissue digestion. Heating and addition of acids continued until residues were white or yellow-white.

The sample residues were dissolved in 5 mL of 2% HNO_3 in distilled water prior to analysis with an ICAP spectrometer.

Standards for testing were made in 2% HNO_3 and were serial dilutions of Fisher Scientific 1,000 ppm solutions. Standard concentrations were: iron analysis - 0.01, 0.05, 0.1, 1, 5, 10, and 40 ppm; manganese analysis - 0.005, 0.01, 0.1, 0.5, 1, and 10 ppm; copper analysis - 0.01, 0.05, 0.1, 0.5, 1.0, and 10 ppm; standard concentrations for zinc were not available.

A zero standard, the 5 ppm iron, 3 ppm zinc, 1 ppm copper, and 1 ppm manganese standards were used to calibrate the spectrometer. Other standards were used as different concentration checks of the calibration curve above and below the high calibration point.

Results of tissue concentration analyses are presented in Tables H1 to H4.

TABLE H1
Tissue Metal Concentration Analyses for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	8	9	10	10
Copper				
Blood plasma	2 ± 0	2 ± 0[b]	2 ± 0	2 ± 0
Brain	3 ± 0	3 ± 0	4 ± 0*	4 ± 0*
Kidney	10 ± 1	9 ± 0	10 ± 1	13 ± 1*
Liver	4 ± 0	4 ± 0	4 ± 0	4 ± 0
Pancreas	2 ± 0	2 ± 0	2 ± 0	2 ± 0
Iron				
Blood plasma	3 ± 0	3 ± 0[b]	3 ± 0	3 ± 0
Brain	27 ± 3	22 ± 1	25 ± 2	26 ± 2
Kidney	123 ± 7	118 ± 3	125 ± 6	133 ± 10
Liver	123 ± 4	114 ± 3	110 ± 7*	105 ± 5*
Pancreas	70 ± 12	54 ± 6	65 ± 13	48 ± 4
Manganese				
Blood plasma	0 ± 0	0 ± 0[b]	0 ± 0	0 ± 0
Brain	1 ± 0	1 ± 0*	1 ± 0**	5 ± 3**
Kidney	1 ± 0	1 ± 0*	1 ± 0**	7 ± 3**
Liver	2 ± 0	3 ± 0**	3 ± 0**	4 ± 0**
Pancreas	2 ± 0	2 ± 0	2 ± 0	3 ± 0**
Zinc				
Blood plasma	2 ± 0	2 ± 0[b]	2 ± 0	2 ± 0
Brain	16 ± 1	16 ± 1	19 ± 1*	21 ± 2**
Kidney	23 ± 1	22 ± 0	25 ± 1	27 ± 2*
Liver	23 ± 1	23 ± 0	23 ± 1	23 ± 1
Pancreas	37 ± 4	47 ± 6	39 ± 5	45 ± 8

TABLE H1
Tissue Metal Concentration Analyses for Rats at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Female				
n	9	10	10	10
Copper				
Blood plasma	2 ± 0[b]	3 ± 0	2 ± 0[c]	2 ± 0
Brain	4 ± 0	4 ± 0	5 ± 0	5 ± 1[c]
Kidney	31 ± 4	35 ± 5	36 ± 5	62 ± 9**
Liver	5 ± 0	5 ± 0	5 ± 0	5 ± 0
Pancreas	3 ± 1	2 ± 0	2 ± 0	3 ± 0
Iron				
Blood plasma	6 ± 1[b]	5 ± 1	15 ± 9[c]	6 ± 1
Brain	32 ± 4	24 ± 1	31 ± 3	27 ± 2[c]
Kidney	209 ± 14	206 ± 13	205 ± 18	229 ± 23
Liver	353 ± 15	327 ± 11	283 ± 10**	236 ± 12**
Pancreas	75 ± 10	54 ± 3	67 ± 5	77 ± 15
Manganese				
Blood plasma	0 ± 0[b]	0 ± 0	0 ± 0[c]	0 ± 0
Brain	1 ± 0	1 ± 0	1 ± 0	1 ± 0[c]
Kidney	1 ± 0	2 ± 0	2 ± 0	5 ± 2**
Liver	3 ± 0	3 ± 0	3 ± 0**	4 ± 0**
Pancreas	3 ± 0	2 ± 0	3 ± 0	3 ± 0
Zinc				
Blood plasma	2 ± 0[b]	1 ± 0	2 ± 0[c]	2 ± 0
Brain	18 ± 1	19 ± 2	21 ± 2	19 ± 1[c]
Kidney	32 ± 2	31 ± 2	34 ± 3	39 ± 4
Liver	26 ± 1	25 ± 0	25 ± 1	26 ± 1
Pancreas	45 ± 5	31 ± 3	40 ± 4	47 ± 4

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Values are given as µg metal/g tissue (mean ± standard error). Statistical tests were performed on unrounded data.
[b] n=10
[c] n=9

TABLE H2
Tissue Metal Concentration Analyses for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	9	9	8
Copper				
Blood plasma	3 ± 0	3 ± 0	3 ± 1	3 ± 1
Brain	16 ± 7	5 ± 1[b]	5 ± 1	5 ± 1
Kidney	10 ± 1	9 ± 1	8 ± 1	12 ± 2
Liver	12 ± 4	12 ± 5	10 ± 4	22 ± 14
Pancreas	3 ± 2	2 ± 0	2 ± 0	2 ± 0
Iron				
Blood plasma	7 ± 1	6 ± 1	7 ± 1	8 ± 2
Brain	37 ± 11	18 ± 2[b]	17 ± 1	24 ± 4
Kidney	139 ± 5	147 ± 5	120 ± 17	140 ± 5
Liver	134 ± 9	138 ± 14	117 ± 5	104 ± 3**
Pancreas	57 ± 3	55 ± 3	395 ± 173	416 ± 256
Manganese				
Blood plasma	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Brain	1 ± 0	1 ± 0[b]	1 ± 0	1 ± 0**
Kidney	1 ± 0	1 ± 0	1 ± 0	2 ± 1**
Liver	2 ± 0	3 ± 0*	3 ± 0**	5 ± 1**
Pancreas	2 ± 0	2 ± 0	1 ± 0	2 ± 0
Zinc				
Blood plasma	3 ± 0	2 ± 0	4 ± 1	3 ± 0
Brain	21 ± 2	16 ± 1[b]	23 ± 4	18 ± 1
Kidney	22 ± 1	22 ± 1	19 ± 3	24 ± 1
Liver	28 ± 2	28 ± 2	28 ± 2	31 ± 5
Pancreas	25 ± 2	27 ± 1	30 ± 5	33 ± 3*

TABLE H2
Tissue Metal Concentration Analyses for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate (continued)

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Female				
n	10	10	9	10
Copper				
Blood plasma	3 ± 0	3 ± 0[c]	4 ± 1	3 ± 0
Brain	5 ± 0	5 ± 0	7 ± 1	5 ± 0
Kidney	31 ± 2	34 ± 3	38 ± 5	57 ± 4**
Liver	8 ± 2	8 ± 1	10 ± 3	11 ± 2
Pancreas	2 ± 0	2 ± 0	2 ± 0	6 ± 3*
Iron				
Blood plasma	13 ± 2	12 ± 1[c]	13 ± 3	11 ± 1
Brain	30 ± 5	22 ± 1	36 ± 13	51 ± 21
Kidney	236 ± 7	221 ± 7	218 ± 7	213 ± 8
Liver	338 ± 21	301 ± 11*	299 ± 12*	261 ± 12**
Pancreas	68 ± 3	877 ± 546	870 ± 532	806 ± 500
Manganese				
Blood plasma	0 ± 0	0 ± 0[c]	0 ± 0	0 ± 0
Brain	1 ± 0	1 ± 0	1 ± 0*	1 ± 0**
Kidney	1 ± 0	2 ± 1	2 ± 1	2 ± 1
Liver	3 ± 0	3 ± 0	4 ± 0**	4 ± 0**
Pancreas	2 ± 0	2 ± 0	2 ± 0	2 ± 0
Zinc				
Blood plasma	2 ± 0	3 ± 0[c]	5 ± 1	3 ± 0
Brain	17 ± 1	18 ± 1	20 ± 3	16 ± 0
Kidney	27 ± 1	27 ± 1	27 ± 1	28 ± 1
Liver	27 ± 1	27 ± 1	27 ± 1	29 ± 1
Pancreas	29 ± 1	28 ± 2	28 ± 3	84 ± 49

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Values are given as µg metal/g tissue (mean ± standard error). Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9

TABLE H3
Tissue Metal Concentration Analyses for Mice at the 9-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	10	10	9
Copper				
Brain	6 ± 0[b]	6 ± 1[b]	6 ± 0[b]	6 ± 0[b]
Kidney	6 ± 0	6 ± 0	6 ± 0	7 ± 0*
Liver	5 ± 0	5 ± 0	5 ± 0	5 ± 0
Pancreas	5 ± 1	4 ± 1	3 ± 0	4 ± 1
Iron				
Brain	22 ± 1[b]	20 ± 2[b]	20 ± 1[b]	20 ± 0[b]
Kidney	92 ± 4	88 ± 6	93 ± 5	98 ± 8
Liver	73 ± 4	65 ± 4	66 ± 3	70 ± 3
Pancreas	103 ± 12	84 ± 9	96 ± 8	139 ± 38
Manganese				
Brain	0 ± 0[b]	1 ± 0*[b]	1 ± 0*[b]	1 ± 0**[b]
Kidney	2 ± 0	2 ± 0**	3 ± 0**	5 ± 0**
Liver	1 ± 0	1 ± 0**	2 ± 0**	4 ± 0**
Pancreas	3 ± 0	2 ± 0	4 ± 0*	6 ± 1**
Zinc				
Brain	16 ± 0[b]	17 ± 1[b]	16 ± 0[b]	16 ± 0[b]
Kidney	22 ± 1	23 ± 1	23 ± 1	24 ± 2
Liver	30 ± 1	30 ± 1	30 ± 0	31 ± 1
Pancreas	53 ± 7	42 ± 4	50 ± 4	53 ± 5
Female				
n	11	10	10	10
Copper				
Brain	6 ± 0[b]	6 ± 0[b]	6 ± 0[b]	7 ± 1[b]
Kidney	6 ± 0	7 ± 0	7 ± 0	7 ± 0
Liver	5 ± 0	5 ± 0	5 ± 0	5 ± 0*
Pancreas	3 ± 0	5 ± 1	4 ± 1	5 ± 2
Iron				
Brain	19 ± 0[b]	19 ± 1[b]	18 ± 0[b]	22 ± 1[b]
Kidney	131 ± 5	142 ± 11	138 ± 12	130 ± 6
Liver	193 ± 6	172 ± 6*	141 ± 5**	123 ± 3**
Pancreas	94 ± 8	95 ± 5	100 ± 8	95 ± 8
Manganese				
Brain	0 ± 0[b]	1 ± 0**[b]	1 ± 0**[b]	1 ± 0**[b]
Kidney	2 ± 0	2 ± 0**	3 ± 0**	5 ± 0**
Liver	1 ± 0	2 ± 0**	3 ± 0**	4 ± 0**
Pancreas	3 ± 0	3 ± 0*	4 ± 0**	5 ± 0**
Zinc				
Brain	16 ± 0[b]	16 ± 0[b]	16 ± 0[b]	17 ± 1[b]
Kidney	22 ± 1	24 ± 2	26 ± 2	25 ± 1
Liver	29 ± 1	29 ± 1	29 ± 1	28 ± 1
Pancreas	52 ± 4	53 ± 3	55 ± 3	58 ± 7

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Values are given as µg metal/g tissue (mean ± standard error). Statistical tests were performed on unrounded data.
[b] n=5

TABLE H4
Tissue Metal Concentration Analyses for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate[a]

	0 ppm	1,500 ppm	5,000 ppm	15,000 ppm
Male				
n	10	10	9	10
Copper				
Brain	6 ± 0[b]	7 ± 0[b]	6 ± 0[b]	6 ± 0[b]
Kidney	31 ± 11	13 ± 3	29 ± 18	8 ± 1
Liver	5 ± 0	5 ± 0	5 ± 0	5 ± 0
Pancreas	4 ± 1	4 ± 1	7 ± 3	5 ± 2
Iron				
Brain	22 ± 1[b]	23 ± 1[b]	22 ± 1[b]	22 ± 1[b]
Kidney	81 ± 3	77 ± 2	74 ± 3	83 ± 4
Liver	102 ± 5	96 ± 6	84 ± 5*	78 ± 3**
Pancreas	92 ± 3	87 ± 4	90 ± 3	86 ± 2
Manganese				
Brain	0 ± 0[b]	1 ± 0**[b]	1 ± 0**[b]	1 ± 0**[b]
Kidney	2 ± 0	3 ± 0*	3 ± 0**	4 ± 1**
Liver[c]	2 ± 1	2 ± 0	2 ± 0**	4 ± 1**
Pancreas	2 ± 0	2 ± 0**	3 ± 0**	3 ± 0**
Zinc				
Brain	19 ± 3[b]	16 ± 0[b]	16 ± 1[b]	16 ± 1[b]
Kidney	33 ± 4	25 ± 2	31 ± 7	22 ± 0*
Liver	32 ± 1	31 ± 1	31 ± 1	32 ± 1
Pancreas	39 ± 3	36 ± 2	42 ± 4	40 ± 1
Female				
n	9	10	9	9
Copper				
Brain	6 ± 0[b]	6 ± 0[b]	7 ± 1[d]	7 ± 0[b]
Kidney	51 ± 19	31 ± 11	13 ± 4	15 ± 4
Liver	6 ± 1	5 ± 0	4 ± 0	5 ± 0
Pancreas	5 ± 1	3 ± 0	4 ± 1	4 ± 1
Iron				
Brain	23 ± 1[b]	22 ± 2[b]	21 ± 0[d]	21 ± 1[b]
Kidney	132 ± 8	107 ± 3**	110 ± 9*	109 ± 7*
Liver	238 ± 11	181 ± 7**	140 ± 12**	134 ± 4**
Pancreas	88 ± 3	87 ± 5	87 ± 6	90 ± 4
Manganese				
Brain	1 ± 0[b]	1 ± 0[b]	1 ± 0[d]	1 ± 1**[b]
Kidney	2 ± 0	2 ± 0*	3 ± 0**	7 ± 3**
Liver	2 ± 0	2 ± 0**	3 ± 0**	4 ± 0**
Pancreas	2 ± 0	2 ± 0	2 ± 0*	3 ± 0**
Zinc				
Brain	17 ± 1[b]	16 ± 1[b]	16 ± 1[d]	16 ± 1[b]
Kidney	40 ± 8	36 ± 5	25 ± 2	26 ± 2
Liver	29 ± 1	29 ± 0	28 ± 1	29 ± 0
Pancreas	35 ± 1	36 ± 2	36 ± 1	38 ± 2

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Values are given as µg metal/g tissue (mean ± standard error). Statistical tests were performed on unrounded data.
[b] n=5
[c] The median values are 0 ppm, 1.2 µg/g; 1,500 ppm, 1.8 µg/g; 5,000 ppm, 2.1 µg/g, 15,000 ppm, 3.4 µg/g.
[d] n=4

APPENDIX I
CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS

CHEMICAL CHARACTERIZATION AND DOSE FORMULATIONS STUDIES

PROCUREMENT AND CHARACTERIZATION OF MANGANESE (II) SULFATE MONOHYDRATE

Manganese (II) sulfate monohydrate was obtained in one lot (003261) from the J.T. Baker Chemical Company (Glen Ellyn, IL). Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). MRI reports on analyses performed in support of manganese (II) sulfate monohydrate studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white, slightly efflorescent crystalline compound, was identified as manganese (II) sulfate monohydrate by infrared and ultraviolet/visible spectroscopy. The infrared spectrum matched a literature reference (Figure I1) (Miller and Wilkins, 1952) and the absence of a signal in the visible spectrum indicated that no manganate (VI) or permanganate (VII) species were present. All spectra were consistent with those expected for the structure.

The purity was determined by elemental analyses, weight loss on drying, chelometric titration, and spark source mass spectroscopy. For chelometric titration, samples were buffered with ammonium/ammonium chloride (NH_3/NH_4Cl) to pH 10, hydroxylamine hydrochloride was added, and the samples were then titrated with standard ethylenediaminetetraacetate (EDTA) solution, with Erichrome Black T used as an indicator.

Elemental analyses for sulfur and hydrogen were in agreement with theoretical values for manganese (II) sulfate monohydrate, while the value obtained for manganese was slightly low. Weight loss on drying indicated 10.6% ± 0.01% water, consistent with a theoretical value of 10.7% for manganese (II) sulfate monohydrate. Spark source mass spectrometry confirmed manganese as the major component and indicated the total concentration of inorganic impurities was equal to 1,235 ppm; the major inorganic impurities were sodium (640 ppm), potassium (120 ppm), and silicon (160 ppm). Chelometric titration indicated a purity of 97.7% ± 0.4%. The overall data indicated that the manganese was in the divalent state and supported a purity of greater than 97%.

The divalent state of manganese is the most common form of this element and is stable in neutral or acid medium. Because of the physical and chemical properties of manganese (II) sulfate monohydrate, no bulk chemical stability studies were performed. The analytical chemistry laboratory recommended the bulk chemical be stored in the dark at room temperature for up to 3 weeks.

Periodic monitoring of the bulk chemical was performed by the study laboratory using chelometric titration methods and by Galbraith Laboratories, Inc. (Knoxville, TN) using elemental analyses; there was no degradation of the bulk chemical during the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared by mixing manganese (II) sulfate monohydrate with feed. All dosed feed was used no more than 3 weeks after it was prepared (Table I1). No direct speciation was performed. However, complete recovery from feed formulations was achieved and other likely species are not soluble in dilute acid which was used for extraction. These findings strongly support the conclusion that the manganese remained in the divalent state.

Homogeneity and stability analyses of 10,000 ppm manganese (II) sulfate monohydrate in feed were conducted by the analytical chemistry laboratory. Aliquots were extracted with reagent grade sulfuric acid diluted to 100 mL with water and centrifuged. The aliquots were treated with 5 mL concentrated sulfuric acid and 4 mL reagent

grade 30% hydrogen peroxide and heated; this step was repeated with additions of hydrogen peroxide until the solutions were colorless. After the aliquots were cooled, 75 mL of an acid mixture of 50 mL sulfuric acid in 660 mL water and 40 mL reagent grade phosphoric acid (85%) was added, the aliquots were heated, and 0.30 g reagent grade potassium periodate was added. After further heating and dilution with water, the absorbance of the samples was measured versus water on a Cary 219 spectrophotometer at 524 nm. Homogeneity was confirmed; stability of the dose formulations was established for 2 weeks in the dark at room temperature and for 1 week exposed to air and light. An additional study confirmed the stability of 1,500 ppm manganese (II) sulfate monohydrate in feed for 21 days in the dark at room temperature.

Periodic analyses of the dose formulations of manganese (II) sulfate monohydrate were conducted at the study laboratory and at the analytical chemistry laboratory, using a similar method as described above. Dose formulations were analyzed once during the 14-day studies, three times during the 13-week studies, and every 2 months during the 2-year studies. All dose formulations for rats and mice were within 10% of the target concentrations throughout the studies (Tables I2 through I4). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated some disagreement with the results obtained by the study laboratory, but were also within 10% of the target concentrations (Table I5).

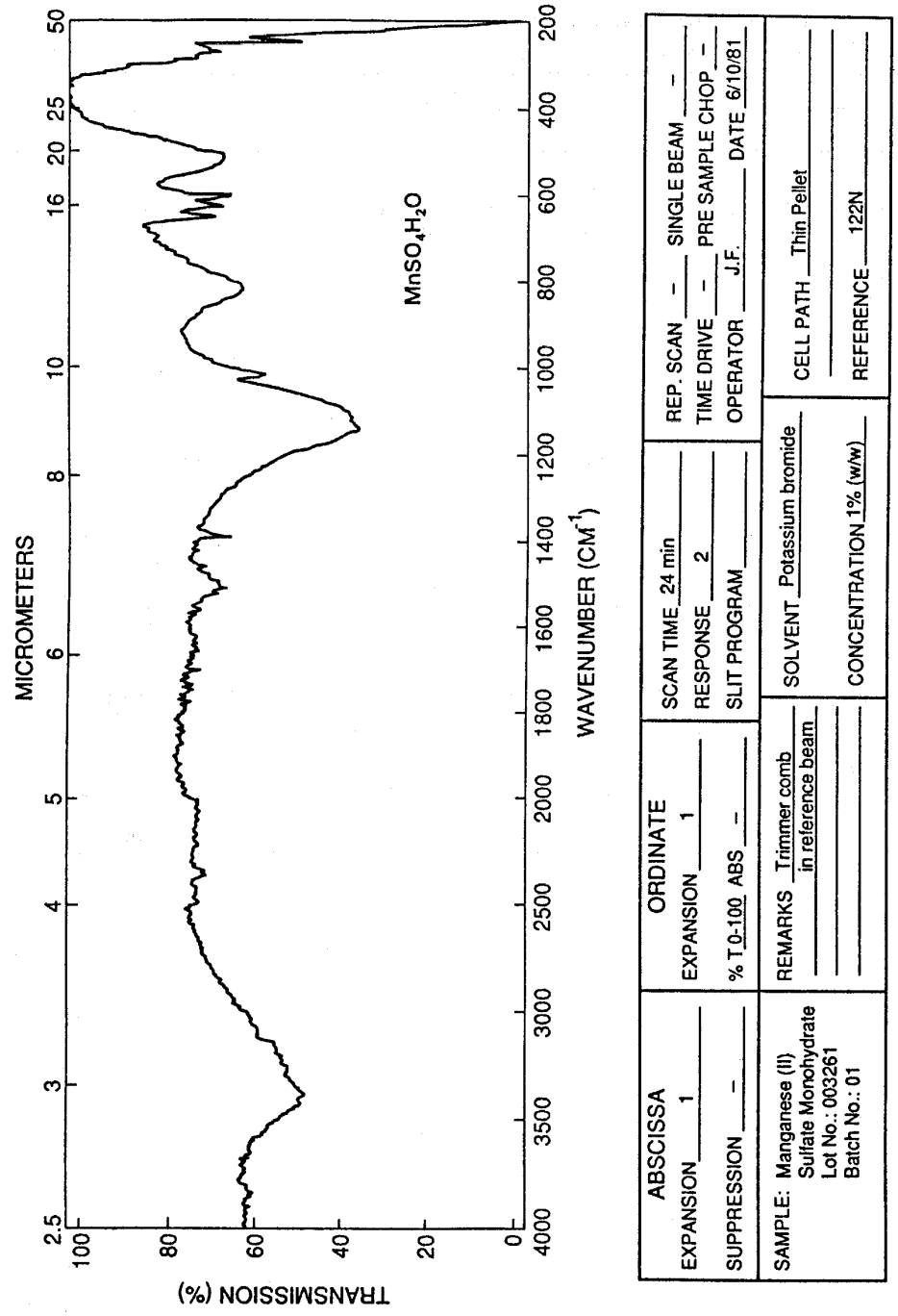

FIGURE I1
Infrared Absorption Spectrum of Manganese (II) Sulfate Monohydrate

TABLE I1
Preparation and Storage of Dose Formulations in the Feed Studies of Manganese (II) Sulfate Monohydrate

14-Day Studies	13-Week Studies	2-Year Studies
Preparation A premix with manganese (II) sulfate monohydrate and feed was prepared by blending with a spatula; premix and remainder of feed was layered in a Patterson-Kelley twin-shell blender and mixed for 15 minutes with an intensifier bar on for the first 5 minutes. Dose formulations were prepared once.	Same as 14-day studies. Dose formulations were prepared weekly.	Same as 13-week studies
Chemical Lot Number 003261	003261	003261
Maximum Storage Time 21 days from date of preparation	Same as 14-day studies	Same as 14-day studies
Storage Conditions Bulk chemical stored in plastic-lined 55-gallon drums at 25° C.	Same as 14-day studies	Stored in plastic buckets with lids in the dark at 25° C.
Study Laboratory Gulf South Research Institute, (New Iberia, LA)	Same as 14-day studies	Battelle Columbus Laboratories, (Columbus, OH)
Referee Laboratory Midwest Research Institute, (Kansas City, MO)	Same as 14-day studies	Same as 14-day studies

TABLE I2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of Manganese (II) Sulfate Monohydrate

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
26 January 1982	28 January 1982	3,130	3,100	−1
			6,250	5,700	−9
			12,500	11,400	−9
			25,000	23,300	−8
			50,000	50,000	0

[a] Results of duplicate analyses

TABLE I3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of Manganese (II) Sulfate Monohydrate

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
24 August 1982	28 August 1982	1,600	1,590	0
		1,600	1,670[b]	+4
		1,600	1,730[c]	+8
		1,600	1,750[d]	+9
		3,130	3,290	+5
		6,250	6,320	+1
		6,250	6,490[b]	+4
		6,250	6,820[c]	+9
		6,250	6,480[d]	+4
		12,500	12,790	+2
		25,000	25,130	+1
		50,000	51,150	+3
		50,000	50,790[b]	+2
		50,000	49,720[c]	−1
		50,000	48,910[d]	−2
28 September 1982	29 September 1982	1,600	1,670	+4
		3,130	3,180	+2
		6,250	6,270	0
		12,500	12,430	−1
		25,000	25,090	0
		50,000	50,690	+1
16 November 1982	17 November 1982	1,600	1,510	−6
		3,130	3,060	−1
		6,250	6,270	0
		12,500	12,770	+2
		25,000	25,500	+2
		50,000	49,640	−1

[a] Results of duplicate analyses
[b] Sample selection from bottom of twin-shell blender
[c] Sample selection from top left of twin-shell blender
[d] Sample selection from top right of twin-shell blender

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Manganese (II) Sulfate Monohydrate

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
18 September 1984	21 September 1984	1,500	1,630	+9
		5,000[b]	4,960	−1
		5,000[c]	4,810	−4
		5,000[d]	4,810	−4
		15,000	14,710	−2
1,2 October 1984	4 October 1984	1,500[b]	1,520	+1
		1,500[c]	1,580	+5
		1,500[d]	1,600	+7
		15,000[b]	14,900	−1
		15,000[c]	15,030	0
		15,000[d]	15,020	0
	11 October 1984[e]	5,000	5,140	+3
27 November 1984	29 November 1984	1,500[b]	1,650	+10
		1,500[c]	1,550	+3
		1,500[d]	1,410	−6
		5,000	5,200	+4
		15,000	14,630	−2
15 January 1985	16 January 1985	1,500	1,530	+2
		5,000	5,050	+1
		15,000	14,930	0
13 March 1985	14 March 1985	1,500	1,630	+9
		5,000	4,960	−1
		15,000	15,010	0
16 May 1985	21 May 1985	1,500	1,570	+5
		5,000	5,320	+6
		15,000	15,610	+4
5 July 1985	9 July 1985	1,500	1,530	+2
		5,000	5,140	+3
		15,000	15,140	+1
30 August 1985	3 September 1985	1,500	1,500	0
		5,000	5,030	+1
		15,000	14,980	0
25 October 1985	28 October 1985	1,500	1,470	−2
		5,000	5,210	+4
		15,000	14,620	−3
27 December 1985	31 December 1985	1,500	1,500	0
		5,000	5,340	+7
		15,000	15,170	+1
13 February 1986	18 February 1986	1,500	1,570	+5
		5,000	5,130	+3
		15,000	15,170	+1

TABLE I4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Manganese (II) Sulfate Monohydrate (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	% Difference from Target
11 April 1986	15 April 1986	1,500	1,520	+1
		5,000	5,050	+1
		15,000	15,240	+2
6 June 1986	9 June 1986	1,500	1,500	0
		5,000	5,030	+1
		15,000	15,030	+0
1 August 1986	4 August 1986	1,500	1,600	+7
		5,000	5,200	+4
		15,000	15,270	+2

[a] Results of duplicate analyses
[b] Sample selection from bottom of twin-shell blender
[c] Sample selection from top left of twin-shell blender
[d] Sample selection from top right of twin-shell blender
[e] Animal room sample

TABLE I5
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Feed Studies of Manganese (II) Sulfate Monohydrate

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
24 August 1982	12,500	12,790	15,900 ± 90
2-Year Studies			
18 September 1984	1,500	1,630	1,450 ± 20
15 January 1985	5,000	5,050	5,020 ± 150
5 July 1985	15,000	15,140	14,670 ± 500
13 February 1986	1,500	1,570	1,550 ± 30
1 August 1986	5,000	5,200	4,980 ± 50

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

APPENDIX J
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE J1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	15.9	227	16.1	220	110	17.0	228	373	17.1	220	1,171
5	14.7	247	18.0	244	111	16.4	251	326	17.8	244	1,095
9	16.1	314	15.2	307	75	13.4	313	213	15.8	306	776
13	17.0	353	17.0	347	74	16.3	351	233	17.0	341	747
18	16.4	386	18.1	375	72	17.6	383	230	17.6	376	701
21	16.2	399	16.8	394	64	16.2	394	206	16.5	386	643
25	16.5	415	16.1	408	59	16.7	411	203	16.1	399	606
28	17.1	431	16.8	423	59	16.5	425	195	18.2	416	657
32	16.1	447	16.6	440	57	17.0	441	193	16.7	432	581
36	16.5	462	16.0	455	53	15.6	453	172	16.3	442	553
44	17.1	472									
48	17.0	480	18.5	474	59	18.9	476	199			
53	16.6	484	16.5	479	52	16.7	479	174	17.3	471	550
57	17.8	499	17.6	487	54	17.1	487	175	18.1	482	562
61	17.3	497	17.4	485	54	17.4	490	178	17.7	481	554
65	16.5	505	16.7	488	51	16.8	493	170	17.4	488	534
69	17.3	509	16.5	487	51	17.5	491	179	17.2	486	532
73	17.8	510	17.4	493	53	17.2	497	173	18.0	493	547
77	16.2	509	16.1	490	49	16.2	496	163	17.1	490	522
81	15.1	498	15.3	479	48	14.6	484	151	16.0	477	505
85	15.9	492	16.1	479	51	15.3	484	158	16.4	478	514
89	14.9	486	14.7	469	47	15.1	469	161	14.0	449	467
93	16.1	472	16.2	451	54	16.2	460	176	15.1	432	524
97	15.0	449	13.8	426	49	15.4	443	174	14.3	409	525
101	15.4	433	14.8	431	52	14.4	423	170	12.7	378	505
104	15.1	402	14.0	402	52	14.4	393	184			
Mean for weeks											
1-13	15.9	285	16.6	279	92	15.7	286	286	16.9	278	947
14-52	16.6	437	17.0	424	60	16.9	426	200	16.9	408	623
53-104	16.2	482	15.9	468	51	16.0	471	171	16.3	463	526

[a] Grams of feed consumed per animal per day
[b] Milligrams of manganese (II) sulfate monohydrate consumed per kilogram body weight per day

TABLE J2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Week	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	12.2	154	12.4	154	120	12.1	153	398	12.6	151	1,249
5	9.4	161	11.1	164	102	9.7	160	302	11.3	160	1,055
9	10.3	186	10.7	190	85	10.6	186	284	10.7	186	864
13	10.8	199	10.7	201	79	10.9	199	273	11.0	198	830
18	10.9	205	11.5	208	83	10.9	206	266	11.0	205	805
21	10.7	210	11.1	213	78	11.2	211	264	11.4	211	812
25	11.0	217	11.5	221	78	11.0	218	253	11.1	217	767
28	10.8	225	11.4	225	76	10.9	222	244	11.7	223	791
32	11.0	232	11.5	236	73	11.3	231	244	11.4	231	738
40	11.2	241	11.3	245	69	11.1	240	232	11.9	243	736
44	11.5	249	12.7	257	74	12.2	251	243			
48	12.3	258				12.8	261	245	12.8	266	724
53	11.9	272	12.3	277	66	12.0	270	221	12.4	277	671
57	11.9	277	12.3	287	64	12.0	279	216	12.7	287	664
61	11.6	286	12.0	294	61	11.7	287	204	12.3	295	625
65	11.8	296	12.2	305	60	12.2	298	205	12.3	303	610
69	13.5	305	13.5	313	65	13.6	306	223	13.5	312	652
73	12.8	311	13.0	320	61	12.7	316	201	12.9	318	608
77	13.2	321	12.3	327	56	13.6	328	207	13.8	329	629
81	12.3	327	12.5	332	57	12.5	333	188	13.3	335	596
85	12.3	335	12.6	339	56	12.7	340	187	13.2	342	581
89	11.9	336	12.2	346	53	12.5	346	180	12.6	346	546
93	13.1	340	12.6	342	55	13.1	345	190	13.2	345	574
97	12.3	334	12.3	335	55	12.7	341	186	12.7	337	568
101	13.1	336	12.5	330	57	13.0	337	193	13.0	333	583
104	11.9	327	11.5	326	53	12.5	336	186	12.5	336	561
Mean for weeks											
1-13	10.7	175	11.2	177	97	10.8	174	314	11.4	174	1,000
14-52	11.2	230	11.6	229	76	11.4	230	249	11.6	228	768
53-104	12.4	314	12.4	320	59	12.6	319	199	12.9	321	605

[a] Grams of feed consumed per animal per day
[b] Milligrams of manganese (II) sulfate consumed per kilogram body weight per day

TABLE J3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Week	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
5	4.1	25.6	4.4	26.1	250	4.3	25.7	845	4.4	25.0	2,663
9	4.8	28.7	4.9	29.2	250	4.7	28.8	811	4.8	27.8	2,567
13	4.5	31.6	5.0	32.5	231	4.3	31.8	681	4.9	30.6	2,399
17	4.3	34.1	4.4	35.2	186	4.4	34.6	630	4.7	32.8	2,172
21	3.9	36.9	3.9	37.9	155	3.9	37.1	532	4.1	35.4	1,744
25	3.9	39.0	4.0	40.1	150	4.0	39.3	507	4.2	37.6	1,668
29	4.0	41.4	4.0	42.1	143	4.0	41.4	482	4.3	39.3	1,624
33	3.9	43.3	4.2	43.7	143	4.1	43.1	478	4.4	41.1	1,607
37	4.5	43.8	4.5	44.5	152	4.6	43.9	523	4.8	42.1	1,720
41	4.4	44.5	4.4	45.2	147	4.4	44.8	494	4.6	43.3	1,591
45	4.2	45.4	4.4	46.5	143	4.4	46.0	475	4.6	44.4	1,569
49	4.3	46.8	4.4	48.2	138	4.4	47.4	465	4.6	45.8	1,502
61	4.4	46.6	4.4	48.0	138	4.7	47.4	492	4.8	46.4	1,566
65	4.2	47.2	4.2	48.5	130	4.1	47.3	435	4.3	46.7	1,371
69	4.8	46.9	4.7	48.2	145	4.7	47.1	499	4.8	45.7	1,581
73	5.0	46.8	4.8	48.1	151	5.0	46.5	540	5.3	45.3	1,766
78	5.0	46.4	4.9	48.3	151	4.8	47.1	511	5.3	46.0	1,714
82	4.6	47.7	4.4	49.3	135	4.2	48.2	438	4.5	46.6	1,449
86	4.4	47.8	4.6	48.9	142	4.5	48.2	463	4.6	46.8	1,484
90	4.5	48.4	4.6	48.9	141	4.5	48.7	462	4.8	47.4	1,528
94	4.6	47.0	4.9	47.6	155	4.7	47.0	502	5.2	46.2	1,685
98	5.2	46.6	5.2	48.1	161	5.1	47.0	546	5.7	45.7	1,870
101	5.2	46.6	5.3	46.4	170	5.0	44.9	562	5.8	45.4	1,917
102	4.7	45.6	5.1	47.0	162	5.1	45.0	571	5.6	41.5	2,036
104	4.7	45.2	5.1	46.3	164	5.1	44.9	572	5.6	44.1	1,916
Mean for weeks											
1-13	4.5	28.6	4.7	29.3	244	4.4	28.8	779	4.7	27.8	2,543
14-52	4.2	41.7	4.3	42.6	151	4.2	42.0	510	4.5	40.2	1,689
53-104	4.7	46.8	4.8	48.0	150	4.7	46.9	507	5.1	45.7	1,683

[a] Grams of feed consumed per animal per day
[b] Milligrams of manganese (II) sulfate monohydrate consumed per kilogram body weight per day

TABLE J4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Manganese (II) Sulfate Monohydrate

Week	0 ppm		1,500 ppm			5,000 ppm			15,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
5	5.0	21.6	5.0	21.7	345	4.9	21.5	1,146	4.8	20.7	3,449
9	4.9	24.3	4.9	24.3	300	4.8	24.3	989	4.4	23.9	2,787
13	5.3	25.6	5.5	26.2	313	5.7	26.3	1,075	5.5	25.5	3,252
17	5.9	28.1	5.2	28.8	271	5.5	28.6	965	5.6	27.7	3,029
21	5.2	30.4	4.9	31.4	233	5.1	31.5	806	5.6	30.5	2,761
25	5.5	33.0	5.2	33.7	230	5.4	33.9	803	5.4	32.8	2,486
29	5.8	36.0	5.1	35.7	214	5.4	36.0	743	6.1	34.5	2,633
33	5.3	38.5	5.1	38.3	201	5.4	38.3	706	6.0	37.0	2,427
37	6.2	40.3	6.1	39.7	229	6.2	39.3	786	7.0	37.9	2,752
41	6.1	41.9	5.4	41.6	193	5.6	40.9	686	5.6	39.0	2,160
45	5.6	43.8	5.1	43.6	177	5.4	42.7	632	5.8	41.6	2,085
49	5.7	46.3	5.3	46.6	171	5.6	45.4	619	6.2	43.6	2,125
54	5.5	47.6	5.2	47.0	166	5.3	45.8	582	6.1	43.8	2,096
57	4.9	47.6	4.9	47.4	155	5.0	46.0	545	5.2	43.9	1,793
61	4.9	48.6	4.7	48.4	146	5.0	46.6	531	5.3	45.0	1,766
65	5.6	49.7	4.8	48.6	149	5.2	47.0	553	5.9	45.3	1,941
69	4.9	49.8	4.9	49.5	148	5.0	47.8	524	5.0	45.8	1,636
73	6.0	51.0	5.2	50.7	154	5.9	48.1	616	6.2	46.3	2,008
78	5.1	50.6	5.1	50.5	153	5.3	48.4	550	5.7	46.3	1,853
82	5.3	52.7	5.2	51.6	150	5.4	50.1	538	5.3	47.9	1,668
86	4.9	53.1	5.0	52.0	144	5.3	50.0	526	5.5	47.8	1,714
90	4.9	53.5	5.1	51.8	147	5.5	50.8	539	5.7	48.3	1,770
94	4.8	53.8	5.0	51.0	147	5.4	50.5	530	5.3	47.7	1,664
98	5.4	52.4	5.3	49.7	161	5.7	48.6	583	5.9	46.2	1,905
102	5.0	51.6	5.1	48.4	159	5.4	47.2	572	5.9	44.4	1,978
104	5.0	50.8	5.1	47.8	161	5.4	46.2	584	5.9	44.3	1,983
Mean for weeks											
1-13	5.1	23.8	5.1	24.1	319	5.1	24.0	1,070	4.9	23.4	3,163
14-52	5.7	37.6	5.3	37.7	213	5.5	37.4	750	5.9	36.1	2,495
53-104	5.1	50.9	5.0	49.6	153	5.3	48.1	555	5.6	45.9	1,841

[a] Grams of feed consumed per animal per day
[b] Milligrams of manganese (II) sulfate monohydrate consumed per kilogram body weight per day

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

TABLE K1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.19 ± 0.57	21.0 – 23.2	20
Crude fat (% by weight)	5.64 ± 0.49	4.6 – 6.3	20
Crude fiber (% by weight)	3.50 ± 0.39	2.8 – 4.7	20
Ash (% by weight)	6.66 ± 0.49	6.0 – 7.9	20
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	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 ± 0.105	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)	9,535 ± 4,094	4,500 – 19,000	20
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.50 – 48.90	8
Thiamine (ppm)	21.85 ± 3.79	19.0 – 37.0	20
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 ± 3.60	23.0 – 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	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 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 – 3,430	8
Minerals			
Calcium (%)	1.11 ± 0.13	0.90 – 1.40	20
Phosphorus (%)	0.91 ± 0.06	0.81 – 1.00	20
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 ± 0.36	1.04 – 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 – 0.780	4

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.72 ± 0.17	0.22 – 0.98	20
Cadmium (ppm)[b]	0.11 ± 0.20	<0.10 – 0.20	20
Lead (ppm)	0.48 ± 0.18	0.14 – 0.87	20
Mercury (ppm)	<0.05		20
Selenium (ppm)	0.36 ± 0.08	0.25 – 0.48	20
Aflatoxins (ppb)	<5.0		20
Nitrate nitrogen (ppm)	14.64 ± 5.39	2.90 – 22.0	20
Nitrite nitrogen (ppm)	0.17 ± 0.20	<0.10 – 1.00	20
BHA (ppm)[c]	2.40 ± 0.88	<2.00 – 5.00	20
BHT (ppm)[c]	1.90 ± 1.12	<1.00 – 4.00	20
Aerobic plate count (CFU/g)[d]	127,745 ± 167,993	3,900 – 570,000	20
Coliform (MPN/g)[e]	296 ± 563	<3.00 – 2,400	20
E. coli (MPN/g)[f]	12.8 ± 33.50	<3.00 – 150.0	20
(MPN/g)[g]	5.6 ± 9.16	<3.00 – 43.00	19
Total nitrosoamines (ppb)[h]	6.71 ± 2.93	3.30 – 13.30	20
N-Nitrosodimethylamine (ppb)[h]	6.12 ± 2.69	3.00 – 13.00	20
N-Nitrosopyrrolidine (ppb)[h]	0.59 ± 0.61	0.30 – 2.70	20
Pesticides			
α-BHC[i]	<0.01		20
β-BHC	<0.02		20
γ-BHC	<0.01		20
δ-BHC	<0.01		20
Heptachlor	<0.01		20
Aldrin	<0.01		20
Heptachlor epoxide	<0.01		20
DDE	<0.01		20
DDD	<0.01		20
DDT	<0.01		20
HCB	<0.01		20
Mirex	<0.01		20
Methoxychlor	<0.05		20
Dieldrin	<0.01		20
Endrin	<0.01		20
Telodrin	<0.01		20
Chlordane	<0.05		20
Toxaphene	<0.1		20
Estimated PCBs	<0.2		20
Ronnel	<0.01		20
Ethion	<0.02		20
Trithion	<0.05		20
Diazinon	<0.1		20
Methyl parathion	<0.02		20
Ethyl parathion	<0.02		20
Malathion[j]	0.11 ± 0.14	0.05 – 0.66	20
Endosulfan I	<0.01		20
Endosulfan 2	<0.01		20
Endosulfan sulfate	<0.03		20

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] One lot contained 0.20 ppm; all other lots contained ≤0.10 ppm.
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony forming units
[e] MPN = most probable number
[f] Lot milled 17 October 1984 contained 150 MPN/g.
[g] Excludes value given in [f].
[h] All values were corrected for percent recovery.
[i] BHC is hexachlorocyclohexane or benzene hexachloride.
[j] Six lots contained more than 0.05 ppm.

APPENDIX L
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Rats

For the 13-week study, samples for viral screening were collected from half of the control animals at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates (Bethesda, MD) for viral titer screening. The following tests were performed on the serum of five male and five female control rats:

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
Compliment Fixation	
RCV (rat coronavirus)	Study termination

At the beginning of the 2-year study, serum samples were collected from 10 female rats for murine virus assays. Serum samples were also collected from five male and five female rats at 6, 12, and 18 months into the study, and from five male and five female rats at terminal sacrifice. Blood from each collection was appropriately processed, shipped to Microbiological Associates, and screened for the following:

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

Mice

For the 13-week study, samples for viral screening were collected from half of the control animals at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates for viral titer screening. The following tests were performed on the serum of four male and five female control mice:

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
ELISA	
MHV (mouse hepatitis virus)	Study termination
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination

Serum samples for viral screening were collected from six male and five female mice and from five mice of each sex on two separate occasions prior to the start of the 2-year study. An additional collection was taken at 8 months into the study for screening of the mouse hepatitis virus only. Serum samples were also collected from sentinel animals at 6, 12, and 18 months into the study, and from five male and five female animals in the 15,000 ppm group at the end of the study. Sera were processed appropriately, shipped to Microbiological Associates, and screened for the following:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM	6, 12, 18, and 24 months
ELISA	
M. arthritidis	6, 12, 18, and 24 months
M. pulmonis	Study initiation, 6, 12, 18, and 24 months
MHV	Study initiation, 6, 8, 12, 18,
PVM	Study initiation, 6, 12, 18, and 24 months
Sendai	Study initiation, 6, 12, 18, and 24 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, 18, and 24 months
MVM	Study initiation, 6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
Immunofluorescent Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 18, and 24 months

Results of serology testing for rats and mice are presented in Table L1.

TABLE L1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of Manganese (II) Sulfate Monohydrate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	4/10	RCV
	8/10	Sendai
Mice		
Study termination	9/9	Sendai
2-Year Studies		
Rats		
Study initiation	0/10	None positive
6 months	1/10	Possible *M. arthritidis*
12 months	0/10	None positive
18 months	0/10	None positive
24 months	2/10	CARB
Mice		
Study initiation	0/10	None positive
6 months	5/10	EDIM
8 months	0/10	None positive
12 months	4/9	EDIM
18 months	4/10	EDIM
24 months	6/10	EDIM
	3/10	*M. arthritidis*