NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF SODIUM DICHROMATE DIHYDRATE

(CAS NO. 7789-12-0)

IN F344/N RATS AND B6C3F1 MICE

(DRINKING WATER STUDIES)

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

July 2008

NTP TR 546

NIH Publication No. 08-5887

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

FOREWORD

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

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

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

NTP Technical Reports are indexed in the NIH/NLM PubMed database and are available free of charge electronically on the NTP website (*http://ntp.niehs.nih.gov*) or in hardcopy upon request from the NTP Central Data Management group at *cdm@niehs.nih.gov* or (919) 541-3419.

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CONTENTS

SUMMARY

Background

Chromium is a metal that exists in a variety of valence states, depending on surrounding conditions and what other atoms it is bound to. The most stable forms are metallic chromium, trivalent chromium (chromium III), and hexavalent chromium (chromium VI). Chromium VI has already been shown to cause cancer when inhaled in the air. Because some compounds containing chromium VI occur as contaminants in drinking water, we studied the effects of sodium dichromate dihydrate in drinking water on male and female rats and mice to identify potential toxic or cancer-related hazards.

Methods

We gave drinking water containing 14.3, 57.3, 172, or 516 mg of sodium dichromate dihydrate per liter of water to groups of 50 male and female rats and female mice for 2 years. Similar groups of male mice were given 14.3, 28.6, 85.7, or 257.4 mg of sodium dichromate dihydrate per liter of water. Control animals received the same tap water with no chemical added. At the end of the study, tissues from more than 40 sites were examined for every animal.

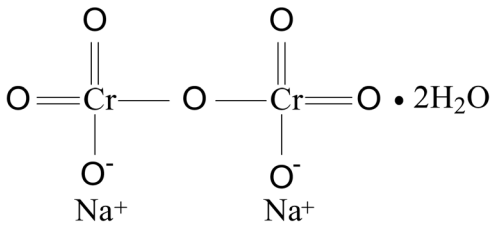
Results

Male and female rats exposed to sodium dichromate dihydrate had carcinomas of the mouth, but none occurred in the control rats. Male and female mice receiving sodium dichromate dihydrate had greatly increased rates of cancer of the small intestine.

Conclusions

We conclude that sodium dichromate dihydrate in the drinking water caused oral cancers in rats and cancer of the small intestine in mice.

ABSTRACT



SODIUM DICHROMATE DIHYDRATE

CAS No. 7789-12-0

Chemical Formula: $Na_2Cr_2O_7 \cdot 2H_2O$ Molecular Weight: 298.0

Synonyms: Chromic acid; dichromic acid, dihydrate; disodium dichromate dihydrate; chromium VI

Sodium dichromate dihydrate is one of a number of inorganic compounds containing hexavalent chromium (Cr VI) found in drinking water source supplies as a contaminant resulting from various industrial processes including electroplating operations, leather tanning, and textile manufacturing. Because of the lack of adequate experimental data on the toxicity and carcinogenicity of hexavalent chromium ingested orally and because hexavalent chromium has been found in drinking water source supplies, the California Congressional Delegation, the California Environmental Protection Agency, and the California Department of Health Services nominated hexavalent chromium to the National Toxicology Program for study. Results of 3-month toxicity studies in F344/N rats and B6C3F1, BALB/c, and *am3*-C57BL/6 mice were reported earlier in NTP Toxicity Report 72. In the current study, male and female F344/N rats and B6C3F1 mice were exposed to sodium dichromate dihydrate (greater than 99.7% pure) in drinking water for 2 years.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate (equivalent to 0, 5, 20, 60, or 180 mg/L chromium) for 2 years (equivalent to average daily doses of approximately 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg body weight for males and 0.7, 2.7, 7, or 20 mg/kg for females). Survival of exposed groups was similar to that of the control groups. Mean body weights of 516 mg/L males and females were less than those of the controls throughout the study. The lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 172 and 516 mg/L rats was less than that by the controls throughout the study. Exposure to sodium dichromate dihydrate caused a microcytic hypochromic anemia in rats that ameliorated with time.

Exposure to sodium dichromate dihydrate resulted in the development of neoplasms of the squamous epithelium that lines the oral mucosa and tongue. The incidences of squamous cell carcinoma in the oral mucosa of 516 mg/L male and female rats were significantly greater than those in the controls. The incidence in 172 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration. The incidences of squamous cell papilloma or squamous

cell carcinoma (combined) of the oral mucosa or tongue of 516 mg/L male and female rats were significantly greater than those in the controls.

Exposure concentration-related nonneoplastic liver lesions were observed in males and females exposed to 57.3 mg/L or greater. These included histiocytic cellular infiltration, chronic inflammation, fatty change (females), basophilic focus (males), and clear cell focus (females). Increased incidences of histiocytic cellular infiltration also occurred in the small intestine (duodenum), mesenteric lymph node, and pancreatic lymph node of males and/or females exposed to 57.3 mg/L or greater.

2-Year Study in Mice

Groups of 50 male mice were exposed to drinking water containing 0, 14.3, 28.6, 85.7, or 257.4 mg/L sodium dichromate dihydrate (equivalent to 0, 5, 10, 30, or 90 mg/L chromium) for 2 years (equivalent to average daily doses of approximately 1.1, 2.6, 7, or 17 mg sodium dichromate dihydrate/kg body weight). Groups of 50 female mice were exposed to drinking water containing 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate (equivalent to 0, 5, 20, 60, or 180 mg/L chromium) for 2 years (equivalent to average daily doses of approximately 1.1, 3.9, 9, or 25 mg/kg). Survival of exposed groups was similar to that of the control groups. Mean body weights of 257.4 mg/L males were less than those of controls from months 2 through 6 of the study, but by the end of the study, the mean body weight of 257.4 mg/L males was only slightly less than that of the control group. Mean body weights of 172 mg/L females were less than those of the controls from months 3 through 12 of the study, and mean body weights of 516 mg/L females were less than those of the controls from month 2 until the end of the study. By the end of the study, the mean body weight of 172 mg/L females was 8% less than that of the controls, and the mean body weight of 516 mg/L females was 15% less than that of the controls. The lower body weights were partly attri-buted to poor palatability of the dosed water and consequent reductions in water consumption. Water consumption by 85.7 and 257.4 mg/L males and 172 and 516 mg/L females was less than that by the controls throughout the study. A treatment-related microcytosis occurred in exposed mice; the mice were less affected than the rats.

The incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum) were increased in exposed groups of male and female mice. The incidences of adenoma of the duodenum in 257.4 mg/L males and 172 and 516 mg/L females were significantly greater than those in the controls. The incidence of carcinoma of the duodenum was significantly increased in 516 mg/L females. The incidence of adenoma of the jejunum in 516 mg/L females was significantly increased compared to that in the controls. When the incidences of adenoma and carcinoma were combined for all sites of the small intestine, the incidences were significantly increased in 85.7 and 257.4 mg/L males and 172 and 516 mg/L females compared to those in the controls. The incidences in 57.3 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration.

The incidences of diffuse epithelial hyperplasia were significantly increased in the duodenum of all exposed groups of male and female mice. The incidences of histiocytic cellular infiltration were significantly increased in the duodenum of 85.7 and 257.4 mg/L males and in 172 and 516 mg/L females. In the jejunum, the incidences of diffuse epithelial hyperplasia and histiocytic cellular infiltration were significantly increased in 516 mg/L females.

The incidences of histiocytic cellular infiltration of the liver in all exposed groups of females, of the mesenteric lymph node in all exposed groups of males and females, and of the pancreatic lymph node of 85.7 and 257.4 mg/L males and 172 and 516 mg/L females were significantly increased.

Tissue distribution studies showed that total chromium concentrations tended to increase with increasing exposure concentration and duration of exposure.

Conclusions

Under the conditions of these 2-year drinking water studies, there was *clear evidence of carcinogenic activity** of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous

cell neoplasms of the oral cavity. There was *clear evidence of carcinogenic activity* of sodium dichromate dihydrate in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum).

Exposure to sodium dichromate dihydrate resulted in histiocytic cellular infiltration in the liver, small intestine, and pancreatic and mesenteric lymph nodes of rats and mice and diffuse epithelial hyperplasia in the small intestine of male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

Summary of the 2-Year Carcinogenesis Studies of Sodium Dichromate Dihydrate

	Male F344/N Rats	Female F344/N Rats	Male B6C3F1 Mice	Female B6C3F1 Mice
Concentrations in drinking water	0, 14.3, 57.3, 172, or 516 mg/L	0, 14.3, 57.3, 172, or 516 mg/L	0, 14.3, 28.6, 85.7, or 257.4 mg/L	0, 14.3, 57.3, 172, or 516 mg/L
Body weights	516 mg/L group less than the control group	516 mg/L group less than the control group	Exposed groups similar to control group	172 and 516 mg/L groups less than control group
Survival rates	28/50, 30/50, 30/49, 36/50, 29/49	33/50, 32/50, 32/50, 36/50, 31/50	33/50, 35/50, 35/50, 38/50, 32/50	37/50, 39/50, 45/50, 42/50, 42/50
Nonneoplastic effects	Liver: infiltration cellular, histiocyte (1/50, 0/50, 2/49, 5/50, 34/49) Small intestine, duodenum: infiltration cellular, histiocyte (0/48, 0/48, 6/47, 36/46, 47/48) Lymph node, mesenteric: infiltration cellular, histiocyte (13/49, 11/50, 30/49, 39/50, 41/49)	Liver: infiltration cellular, histiocyte (1/50, 5/50, 21/50, 42/50, 47/50) Small intestine, duodenum: infiltration cellular, histiocyte (0/46, 0/49, 1/48, 30/46, 47/50) Lymph node, mesenteric: infiltration cellular, histiocyte (21/50, 18/50, 27/50, 36/50, 42/50) Lymph node, pancreatic: infiltration cellular, histiocyte (17/29, 20/36, 23/30, 32/34, 27/33)	Small intestine, duodenum: epithelium, hyperplasia, diffuse (0/50, 11/50, 18/50, 42/50, 32/50); infiltration cellular, histiocyte (0/50, 2/50, 4/50, 37/50, 35/50) Lymph node, mesenteric: infiltration cellular, histiocyte (14/47, 38/47, 31/49, 32/49, 42/46) Lymph node, pancreatic: infiltration cellular, histiocyte (0/5, 2/13, 2/10, 5/8, 12/16)	Liver: infiltration cellular, histiocyte (2/49, 15/50, 23/50, 32/50, 45/50) Small intestine, duodenum: epithelium, hyperplasia, diffuse (0/50, 16/50, 35/50, 31/50, 42/50); infiltration cellular, histiocyte (0/50, 0/50, 4/50, 33/50, 40/50) Small intestine, jejunum: epithelium, hyperplasia, diffuse (0/50, 2/50, 1/50, 0/50, 8/50); infiltration cellular, histiocyte (0/50, 0/50, 0/50, 2/50, 8/50) Lymph node, mesenteric: infiltration cellular, histiocyte (3/46, 29/48, 26/46, 40/50, 42/50) Lymph node, pancreatic: infiltration cellular, histiocyte (0/14, 1/12, 2/15, 7/14, 8/13)

Summary of the 2-Year Carcinogenesis Studies of Sodium Dichromate Dihydrate

	Male F344/N Rats	Female F344/N Rats	Male B6C3F1 Mice	Female B6C3F1 Mice
Neoplastic effects	Oral mucosa: squamous cell carcinoma (0/50, 0/50, 0/49, 0/50, 6/49) Oral mucosa or tongue: squamous cell papilloma or squamous cell carcinoma (0/50, 1/50, 0/49, 0/50, 7/49)	Oral mucosa: squamous cell carcinoma (0/50, 0/50, 0/50, 2/50, 11/50) Oral mucosa or tongue: squamous cell papilloma or squamous cell carcinoma (1/50, 1/50, 0/50, 2/50, 11/50)	Small intestine, duodenum: adenoma (1/50, 0/50, 1/50, 5/50, 15/50) Small intestine, duodenum, jejunum, or ileum: adenoma (1/50, 1/50, 1/50, 5/50, 17/50); carcinoma (0/50, 2/50, 1/50, 3/50, 5/50); adenoma or carcinoma (1/50, 3/50, 2/50, 7/50, 20/50)	Small intestine, duodenum: adenoma (0/50, 0/50, 2/50, 13/50, 12/50); carcinoma (0/50, 0/50, 0/50, 1/50, 6/50) Small intestine, jejunum: adenoma (0/50, 1/50, 0/50, 2/50, 5/50) Small intestine, duodenum, jejunum, or ileum: adenoma (0/50, 1/50, 2/50, 15/50, 16/50); carcinoma (1/50, 0/50, 2/50, 3/50, 7/50); adenoma or carcinoma (1/50, 1/50, 4/50, 17/50, 22/50)
Level of evidence of carcinogenic activity	Clear evidence	Clear evidence	Clear evidence	Clear evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on sodium dichromate dihydrate on May 16, 2007, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On May 16, 2007, the draft Technical Report on the toxicology and carcinogenesis studies of sodium dichromate dihydrate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. M.J. Hooth, NIEHS, introduced the toxicology and carcinogenesis studies of sodium dichromate dihydrate by discussing the uses of chromium, the rationale for study, and the short-term studies; describing the design of the long-term studies; and reporting on survival and body weight effects and compound-related neoplastic and nonneoplastic lesions. Dr. R.A. Herbert, NIEHS, described the histopathologic details of several of the observed lesions. The proposed conclusions for the 2-year studies were *clear evidence of carcinogenic activity* of sodium dichromate dihydrate in male and female F344/N rats and *clear evidence of carcinogenic activity* of sodium dichromate dihydrate in male and female B6C3F1 mice.

Dr. Walker, the first principal reviewer, agreed with the proposed conclusions. He differed with one of the public responses to the report that suggested there should be more discussion of sites with decreased tumor incidence, noting that the primary purpose of the study was to detect carcinogenic responses. He felt the discussion of other studies, some with conflicting results, was balanced. He felt it was noteworthy that, although chromium was detected at other tissue sites, the main carcinogenic response in mice was in the small intestine, primarily in the duodenum and decreasing farther down the intestinal tract.

Dr. Novak, the second principal reviewer, also agreed with the proposed conclusions. He inquired whether any clinical chemistry panel had been performed to detect changes in hormone levels. He asked if any of the observed histiocytic cellular infiltration could be associated with inflammation.

Dr. Sikka, the third principal reviewer, agreed with the proposed conclusions and inquired if there was any explanation for the difference in the organ-specific susceptibility of the two rodent species to the carcinogenic effects of sodium dichromate dihydrate.

Dr. Hooth noted that a couple of tumors were seen in the ileum of male mice, and Dr. Walker replied that it was still interesting that the numbers of tumors did decrease progressively down the intestinal tract. In response to Dr. Novak, Dr. Hooth replied that because this was a study of hexavalent chromium, examinations of the effects of trivalent chromium on lipid or carbohydrate metabolism were not performed. Regarding the histiocytic cellular infiltration, Dr. Herbert replied that these were not granulomas, with some causative agent like bacteria or fungus or necrosis, and no additional inflammatory cells were seen in association with the infiltration. In response to Dr. Sikka, Dr. Hooth replied that in a survey of 21 NTP studies that caused neoplasms of the oral cavity in rats, none caused similar neoplasms in male mice and only one in female mice. Dr. Hooth added that further studies were underway to characterize the absorption of chromium in the stomach and intestine.

Dr. Mirsalis inquired if the palatability of the chemical may have affected water consumption or body weights of the animals. Dr. Cattley asked about the sampling procedures for oral cavity lesions and if all the carcinomas were detected by gross examination. Dr. Herbert replied that a reexamination of all the tissue samples provided confidence that all potential lesions were detected.

Dr. Kirkvliet said that written comments had been submitted by six organizations: the Sapphire Group; the Department of Health Sciences of the University of Genoa, Italy; the Interfaith Community Organization; Exponent, Inc.; Consulting Scientists; and the Environmental Working Group.

Mr. T. McKee, representing the Interfaith Community Organization of New Jersey, said the NTP had produced a well-designed and meticulously executed study and an insightful and illuminating report. He urged that the report be completed expeditiously in light of the need for the study results by regulatory agencies.

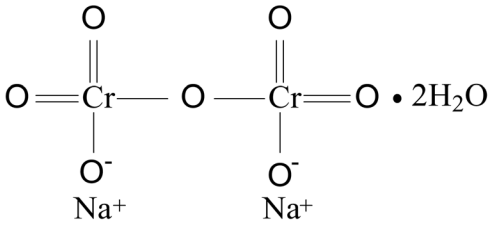
Dr. D.M. Proctor, representing Tierra Solutions, Inc., noted that the chromium concentrations in the NTP

study were 50 to 100 times higher than the existing drinking water standards. She indicated that no epidemiology studies in the literature indicated increases in oral cavity or intestinal tumors as a result of exposure to chromium. She also claimed that the body weights and water consumption of the study animals were significantly lower than for the control groups and suggested that lower palatability and dehydration may have affected the physiology of the exposed animals. She speculated that dehydration could lead to lower production of saliva, which might affect the ability of animals to reduce chromium VI.

Dr. Walker inquired if the water consumption was indeed altered significantly in this study. Dr. Hooth discussed the criteria for the diagnosis of dehydration, which included clinical observations of circulatory hypo-volemia, including loss of skin turgor, dry mucous membranes, retraction of eyes, and even shock and increases in clinical pathology parameters such as albumin, hematocrit, urea nitrogen, or urine specific gravity. None of these indicators was observed in the present study. Dr. Hooth also presented plots showing that only one dosed group of male rats varied by more than 10% from controls late in the study, and that water consumption on a body weight basis was nearly identical for exposed and control rats.

Dr. Walker moved, and Dr. Soper seconded, that the conclusions be accepted as written. The motion was approved unanimously with seven votes.

INTRODUCTION



SODIUM DICHROMATE DIHYDRATE

CAS No. 7789-12-0

Chemical Formula: $Na_2Cr_2O_7 \cdot 2H_2O$ Molecular Weight: 298.0

Synonyms: Chromic acid; dichromic acid, dihydrate; disodium dichromate dihydrate; chromium VI

CHEMICAL AND PHYSICAL PROPERTIES

Sodium dichromate dihydrate exists in solid form as reddish to bright orange crystals, which become anhydrous when heated to approximately 100° C. The anhydrous form has a melting point of 356.7° C (*Merck*, 1996). The water solubility of sodium dichromate dihydrate is 230 g/L at 0° C. Chromium is a group 6 transition metal and occurs in the earth's crustal rock at a concentration averaging 122 ppm. It has six oxidation states. The most stable states are metallic chromium (Cr), trivalent chromium (Cr III), and hexavalent chromium (Cr VI). Cr VI is typically present in complexes with halide (chromyl chloride) and oxygen ligands (chromium trioxide, chromate, dichromate). Sodium dichromate dihydrate is one of a number of inorganic compounds that contain Cr VI. Other representatives of this class of compounds include calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate. The physical properties and water solubility of these compounds vary considerably. In aqueous solution, dichromate and chromate are in equilibrium. The form of Cr VI present depends on pH and concentration. At physiological pH and millimolar concentrations, Cr VI exists primarily as the chromate ion (Hamilton and Wetterhahn, 1988). The proportion existing as dichromate increases as the concentration increases and/or the pH is decreased.

Cr VI is easily reduced to Cr III in acidic solutions containing organic molecules such as proteins, DNA, or glutathione. Glutathione is also capable of reducing Cr VI at neutral pH at a slower rate than under acidic conditions (Zhitkovich, 2005).

PRODUCTION, USE, AND HUMAN EXPOSURE

Metallic chromium is produced by reduction of chromite ore. Sodium dichromate is produced by roasting chromite ore with soda ash and is used for the production of other chromium compounds (Hartford, 1979; Westbrook, 1979). Metallic chromium is used in the metallurgical industry for the production of stainless steel and ferrous and nonferrous alloys. The major uses of chromium in the chemical and manufacturing industries include the production of chromium pigments and in metal finishing, leather tanning, and wood preservation (Barnhart, 1997). Chromium enters the environment from combus-

tion processes and ore processing mainly as chromium (III) oxide. Cr VI has been detected in fly ash from power plants (Stern, 1982). Both Cr III and Cr VI enter water resources by leaching from soil or from industrial contamination (Pellerin and Booker, 2000) as well as from atmospheric fallout. A Cr VI concentration as high as 580 µg/L was found in a groundwater monitoring well in Hinkley, California (Pellerin and Booker, 2000). Detectable levels of hexavalent chromium have been reported in approximately 30% of the drinking water sources monitored in California, which has a 1 µg/L detection limit for purposes of reporting (CDHS, 2004); 87% of those sources had concentrations ranging from 1 to 10 µg/L. The United States Environmental Protection Agency has set a maximum contaminant level of 100 µg/L for total chromium in drinking water (ATSDR, 2000). The California state limit is 50 µg/L of total chromium in drinking water (CDHS, 2004). Human exposure to chromium occurs through food, water, and air. The highest exposure to Cr VI occurs occupationally to workers involved in chrome plating, chromate production, and stainless steel welding. Exposure in these situations is typically by inhalation or dermal contact. Dermal exposure to chromium compounds results in irritation and ulceration of the skin and causes allergic contact dermatitis in sensitized individuals. Additional information on human exposure to chromium and chromium compounds can be found in the Toxicological Profile for Chromium (ATSDR, 2000).

Absorption, Distribution, Metabolism, and Excretion

Chromium and chromium compounds are found to be absorbed after oral, dermal, or inhalation exposure (Wahlberg and Skog, 1965; Wahlberg, 1970; Kerger *et al.*, 1997; Mancuso, 1997). Current analytical procedures cannot differentiate between the oxidation states of chromium in biological tissues so total chromium content is measured in excreta and tissues. Most studies of absorption of Cr III or Cr VI after oral administration to rodents found that only 1% or 2% of the administered dose is bioavailable, whereas similar studies with humans report somewhat higher numbers (ATSDR, 2000), particularly for Cr VI. It is thought that Cr VI is poorly absorbed when ingested due to its rapid reduction to less soluble Cr III in the presence of food and the acidic environment encountered in the stomach (Sutherland *et al.*, 2000). Cr III is less efficiently absorbed than Cr VI compounds, and this is attributed to a difference in their respective methods of transport into cells. Cr VI enters cells by facilitated diffusion via nonspecific anion channels, while Cr III enters cells by passive diffusion or phagocytosis of precipitates resulting in much lower uptake (ATSDR, 2000).

Human and animal studies show that chromium is widely distributed in the body after exposure to Cr VI, with liver, kidney, spleen, and bone having higher concentrations than other tissues (MacKenzie *et al.*, 1959; Coogan *et al.*, 1991; Kargacin *et al.*, 1993; Costa, 1997; Mancuso, 1997). Rats consuming up to 10 mg/L Cr VI as potassium chromate in drinking water for 44 weeks had elevated chromium levels in bone, kidney, liver (females only), and testis (males only) (Sutherland *et al.*, 2000). Other studies showed that chromium can cross the placenta (Casey and Hambidge, 1984; Saxena *et al.*, 1990; Kirpnick-Sobol *et al.*, 2006). Higher tissue chromium levels were found in rats receiving Cr VI orally than in those receiving an equivalent dose of Cr III (Costa, 1997). Following uptake by erythrocytes and tissues, Cr VI is thought to undergo reduction to Cr III intracellularly, primarily by ascorbate (Sugiyama, 1992).

Ingested chromium is excreted primarily in the feces because of its poor absorption. Absorbed chromium appears to be primarily excreted in the urine (Donaldson and Barreras, 1966; Sayato *et al.*, 1980). O'Flaherty (1993, 1996) has constructed a physiologically based pharmacokinetic model for Cr VI compounds in the rat, and the ATSDR (2000) has outlined distribution and clearance models for Cr III in humans.

Prior to selection of rats and mice as the test species for the studies in the current Technical Report, the National Toxicology Program (NTP) conducted a comparative absorption study of sodium dichromate dihydrate (Cr VI) administered in the drinking water to F344/N rats, B6C3F1 mice, and Hartley guinea pigs (NTP, 2007a). Concentrations of total chromium were determined in blood and kidney. Guinea pigs were chosen for study, in addition to rats and mice, because they more closely resemble humans in that they do not have a forestomach and they require vitamin C (a reducing agent) in their diet. In all three species, chromium in blood and kidney increased with exposure concentration (NTP, 2007a). Although differences were seen in the absolute amounts of chromium in kidney and blood, uptake as a function of exposure concentration did not appear to differ qualitatively in guinea pigs when compared to rats and

mice. This suggests that the presence of a forestomach did not fundamentally alter the handling of Cr VI in the gastrointestinal tract. Kidney chromium concentration was highest in rats, followed by mice and guinea pigs. For blood, guinea pigs had the highest concentrations, followed by mice and rats. The concentrations of chromium in blood and kidney were in general agreement with values observed by Sutherland *et al.* (2000).

TOXICITY

Cr III is an essential trace element. The recommended daily intake of Cr III for adults ranges between 25 and 45 µg (IOM, 2001). Cr III deficiency contributes to glucose intolerance and diabetes mellitus (Type 2). Chromium appears to increase sensitivity to insulin. The mechanism involves increased insulin binding through increasing the number of insulin receptors and increasing insulin receptor phosphorylation in the presence of insulin and a low molecular weight chromium complex (Anderson, 1998). Cr III displays little to no toxicity in humans and animals (ATSDR, 2000).

The toxicity of Cr VI in humans and animals has been reviewed extensively (Costa 1997; USEPA, 1998; ATSDR, 2000; Costa and Klein, 2006). More recently, the NTP performed 3-month studies of sodium dichromate dihydrate in male and female F344/N rats and B6C3F1 mice to aid in the design and dose selection for these 2-year carcinogenicity studies of sodium dichromate dihydrate (NTP, 2007a). Rats and mice were given drinking water containing 0, 62.5, 125, 250, 500, or 1,000 mg sodium dichromate dihydrate/L for 3 months. All rats and mice survived to the end of the studies. Final mean body weights and body weight gains were less than those of controls in male rats exposed to 500 or 1,000 mg/L, female rats exposed to 1,000 mg/L, and in male and female mice exposed to 125 mg/L or greater. Exposure to sodium dichromate dihydrate caused a microcytic hypochromic anemia in rats and mice, but the severity was less in mice. The primary nonneoplastic lesions were observed in the glandular stomach of rats exposed to 1,000 mg/L and included focal ulceration, regenerative epithelial hyperplasia, and squamous epithelial metaplasia. Histiocytic cellular infiltration was observed in the duodenum of rats and mice, the liver of female rats, and the mesenteric lymph nodes of mice exposed to 125 mg/L or greater. Histiocytic cellular infiltration was also observed in the pancreatic lymph nodes of rats exposed to 1,000 mg/L. All exposed groups of mice had significantly increased incidences of epithelial hyperplasia of the duodenum.

The NTP examined the potential of sodium dichromate dihydrate exposure via drinking water to modulate immune function in female B6C3F1 mice, F344/N rats, and Sprague-Dawley rats by conducting 28-day range finding studies (NTP, 2007b,c,d). Sodium dichromate dihydrate exposure concentrations in the mice were 0, 15.6, 31.25, 62.5, 125, or 250 mg/L and in the rats were 0, 14.3, 57.3, 172, or 516 mg/L. No significant signs of overt toxicity were observed in these studies. Reductions in final mean body weight and body weight gain were observed in 250 mg/L B6C3F1 mice and 516 mg/L Sprague-Dawley rats. F344/N and Sprague-Dawley rats in the 172 and 516 mg/L groups consumed significantly less water than the control animals, which was attributed to poor palatability of the drinking water solutions. Sodium dichromate dihydrate exposure did not produce significant changes in organ weights. In 250 mg/L mice, some of the erythroid parameters were significantly decreased (5% to 7%) including hemoglobin, hematocrit, mean cell volume, and mean cell hemoglobin. In rats, hematology parameters were not affected. Sodium dichromate dihydrate exposure produced minimal effects in the various immunological parameters evaluated in mice and rats. There were no biologically meaningful changes in spleen cell numbers or in the percentage and absolute number of B cells, T cells, $CD4^+$ T cells, $CD8^+$ T cells, natural killer cells, and macrophages. Sodium dichromate dihydrate exposure did not produce a reproducible significant effect on the IgM antibody-forming cell response to sheep red blood cells or to the T-dependent antigen keyhole limpet hemocyanin. There was no effect of sodium dichromate dihydrate on cell-mediated immunity and natural killer cells evaluated using anti-CD3 antibody mediated T cell proliferation and the cytotoxic assay of YAC-1 cells, respectively.

Renal effects observed in rats administered Cr VI (as potassium chromate, 13.5 mg/kg per day for 20 days) by gavage included increased accumulation of lipid, triglycerides, and phospholipids in different regions of the kidney than in controls and inhibited kidney membrane enzymes (alkaline phosphatase, acid phosphatase, glucose-6-phosphatase, and lipase) (Kumar and Rana, 1982, 1984). Oliguria and proteinuria were also observed in rats exposed to Cr VI (as sodium chromate, 100 mg/kg per day for 28 days) in drinking water (Diaz-Mayans *et al.*, 1986).

A number of studies have reported reproductive effects in rats and mice orally exposed to Cr VI. These studies utilized similar exposure concentrations (250 to

1,000 mg/L) of potassium dichromate provided in the drinking water of female rats and mice prior to mating or during gestation. Cr VI exposure consistently resulted in increased preimplantation and postimplantation losses, resorptions, and stillbirths and decreased numbers of corpora lutea and numbers of fetuses (live and dead) (Trivedi *et al.*, 1989; Junaid *et al.*, 1996a,b; Kanojia *et al.*, 1996, 1998). In addition, these studies provided evidence that Cr VI is a developmental toxicant in rats and mice. Fetuses were consistently reported to have retarded development, decreased fetal body weight and crown-rump length, and higher incidences of subdermal hemorrhagic patches and kinky short tails. There was also a significant reduction in ossification in caudal, parietal, and interparietal bones of the fetuses.

In contrast, results of NTP studies in BALB/c mice and Sprague-Dawley rats showed that potassium dichromate was not a reproductive toxicant when administered in the diet for 9 weeks followed by an 8-week recovery period (NTP, 1996a,b). However, rats and mice administered potassium dichromate by diet (8.4 and 9.8 mg Cr VI/kg body weight per day for male and female rats, respectively; 32.2 and 48 mg Cr VI/kg body weight per day for male and female mice, respectively) showed reduced mean red cell volume and mean red cell hemoglobin. This effect was not seen at lower exposure concentrations. Similar decreases were seen in a multigeneration study of mice given potassium dichromate in the diet. The decreases were seen in BALB/c males receiving Cr VI at 16 mg/kg per day and 36.7 mg/kg per day and BALB/c females receiving Cr VI at 7.8 mg/kg per day (NTP, 1997).

Toxicity of Cr VI has not been confirmed in all animal studies. In a drinking water study, rats given Cr VI (as potassium chromate, 3.6 mg/kg per day) for 1 year showed no evidence of hepato- or nephrotoxicity and no alteration in hematology or clinical chemistry parameters (MacKenzie *et al.*, 1958).

CARCINOGENICITY

Exposure to Cr VI compounds by inhalation has long been recognized as carcinogenic to humans. The United States Department of Health and Human Services, the United States Environmental Protection Agency, and the International Agency for Research on Cancer classified Cr VI compounds as human carcinogens based on increased incidences of lung cancers in workers in the chromium industry and in experimental animals exposed to these compounds by inhalation (IARC, 1990; Cohen *et al.*, 1993; NTP, 1998). The specific compounds listed as carcinogens include calcium chromate, chromium trioxide, lead chromate, strontium chromate, and zinc chromate.

Although Cr VI compounds are demonstrated carcinogens by the inhalation route, it has been suggested that the reductive capacity of the gut would be adequate to prevent Cr VI from being a carcinogen when ingested (De Flora *et al.*, 1997; Proctor *et al.*, 2002). Little data exist regarding health effects resulting from ingestion of Cr VI compounds. A review of the few epidemiological studies that evaluated populations that were exposed to Cr VI in drinking water or in soil or slag fill concluded that these studies did not provide definitive evidence of an increase in cancer incidence or mortality rates (Proctor *et al.*, 2002). However, a retrospective mortality study of a population living near a chromium smelting plant in the People's Republic of China found increased incidences of lung and stomach tumors as compared to those of the general population. The authors did not estimate exposure levels nor was the size of the population specified (Zhang and Li, 1987; ATSDR, 2000). More recently, Sedman *et al.* (2006) reevaluated the findings of this study as well as additional reports by the investigators and confirmed the significant increases in lung and stomach neoplasms.

Only one lifetime animal carcinogenicity study was identified in the literature in which hexavalent chromium was administered in the drinking water. Three generations of NMRI mice were exposed to 9 mg Cr VI/kg body weight administered in the drinking water as potassium chromate. In treated mice, two of 66 females developed forestomach carcinomas and nine of 66 females and one of 35 males developed forestomach papillomas. Forestomach papillomas were observed in the vehicle controls (2 of 79 females and 3 of 47 males), but no carcinomas were observed in the vehicle controls. Most of the tumors were observed in the F_0 generation. The increased incidence of forestomach tumors in the treated mice was not statistically significant (Borneff *et al.*, 1968; ATSDR, 2000). However, when benign and malignant forestomach neoplasms were combined in the three generations of female mice, there was a statistically significant increase compared to the control group (Sedman *et al.*, 2006). This study has several limitations including high early mortality in the F_0 generation as a

result of ectromelia (mousepox) virus.

Davidson *et al.* (2004) showed that exposure to potassium chromate in drinking water enhanced the incidence of ultraviolet radiation-induced skin tumors in a hairless mouse model. Female SK1-hrBR mice were exposed for 6 months to ultraviolet light at a constant energy of 1.18 kJ/m^2 and to potassium chromate in drinking water at 0.5, 2.5, or 5.0 mg/L. There was an exposure concentration-dependent increase in the number of skin neoplasms in mice exposed to ultraviolet light and potassium chromate, which was statistically significant at the two highest chromate doses. The authors concluded that Cr VI can increase susceptibility to carcinogenesis following drinking water exposure.

Trivalent chromium exposure is not considered to pose a significant cancer risk in humans or in animals (ATSDR, 2000). There was no evidence of carcinogenicity in male or female Becton Dickinson rats fed diets containing up to 5% chromium oxide (2,040 mg Cr III/kg per day), 5 days per week for 2 years, or in the offspring of rats treated for 60 days prior to gestation and during gestation, after 600 days of observation (Ivankovic and Preussmann, 1975).

Genetic Toxicity

Most studies measuring genetic damage endpoints in humans occupationally exposed to atmospheric hexavalent chromium reported results consistent with chromium-induced chromosomal damage (IARC, 1990). In several studies, elevated frequencies of sister chromatid exchanges and chromosomal aberrations were reported in lymphocytes of Cr VI-exposed workers. Correlations were documented in some of these studies between the concentrations of chromium in the workplace or the duration of exposure and the amount of genetic damage detected. In recent studies, evaluation of biological samples including exfoliated buccal cells and peripheral lymphocytes from workers (electroplaters or welders) exposed to chromium by inhalation revealed significant increases in micronuclei, which are indicators of structural and numerical chromosome changes (Vaglenov *et al.*, 1999; Benova *et al.*, 2002; Danadevi *et al.*, 2004). Chromosomal aberrations have also been observed in cultured human bronchial epithelial cells exposed to soluble sodium chromate (VI) and particulate lead chromate (VI) (Wise *et al.*, 2006). No studies were located regarding genotoxic effects in humans after oral exposure to hexavalent chromium compounds.

Hexavalent chromium is genotoxic in a number of *in vitro* and *in vivo* test systems, although responses are somewhat variable depending on protocol details and the type of chromium salt that is assayed. Overall, the data clearly indicate that in appropriate test systems, Cr VI exposure results in increased frequencies of gene mutations and chromosomal alterations. The extensive literature on the mutagenicity of chromium compounds has been reviewed by a number of authors, most recently by IARC (1990) and by De Flora *et al.* (1990). To summarize the findings briefly, positive results were obtained *in vitro* with Cr VI compounds in gene mutation tests using *Salmonella typhimurium* or *Escherichia coli* (most recently, positive results reported in NTP, 2007a); forward mutation and mitotic gene conversion assays in yeast; mammalian cell (including human cell lines) chromosomal damage assays that measured increases in sister chromatid exchanges, chromosomal aberrations, or micronuclei; mutation induction at the tk locus in L5178Y mouse lymphoma cells; and tests for induction of DNA strand breaks or DNA synthesis inhibition in a variety of mammalian cells. *In vivo*, positive results were seen in short-term assays in laboratory rodents for induction of chromosomal damage and micronuclei following administration of Cr VI by intraperitoneal injection. Comparative micronucleus assays in various strains of male and female mice (ms, BDF1, CD-11, ddY, ICR) revealed no sex- or strain-related differences in overall results (CSGMT, 1986, 1988). Route of administration was shown to be a factor, however, with intraperitoneal injection administration (up to 80 mg/kg) of potassium dichromate giving positive results and oral gavage (up to 320 mg/kg) giving negative results in two strains (MS/Ae and CD-1) of male mice (Shindo *et al.*, 1989).

Recent results from *in vivo* chromosomal damage assays in animals using drinking water as the route of administration have given mixed results. De Flora *et al.* (2006) measured the frequency of micronucleated erythrocytes in peripheral blood of BDF1 or Swiss mice exposed to sodium dichromate dihydrate or potassium dichromate in drinking water (up to 500 mg chromium VI/L for 210 days); no alterations in the frequencies of micronucleated erythrocytes were seen and the authors suggested that the absence of genotoxicity by this route of exposure provided evidence for gastrointestinal detoxification of Cr VI. In contrast, exposure of adult BDF1 or Swiss mice to Cr VI by intraperitoneal injection (50 mg/kg potassium dichromate or sodium dichromate dihydrate) produced significant increases in micronucleated erythrocytes (De Flora *et al.*, 2006). NTP peripheral

blood micronucleus studies conducted in B6C3F1, BALB/c, and *am3*-C57BL/6 mice with sodium dichromate dihydrate administered in drinking water for 3 months gave mixed results (NTP, 2007a); significant increases in micronucleated erythrocytes were seen only in *am3*-C57BL/6 mice. Kirpnick-Sobol *et al.* (2006) reported that exposure of pregnant mice (C57BL/6J p^{un}/p^{un}) to either potassium dichromate (Cr VI; 62.5 or 125.0 mg/L) or chromium (III) chloride (1,875 or 3,750 mg/L) in drinking water during gestational days 10 to 20 resulted in significant increases in the frequencies of large-scale DNA deletions in their pups examined at 20 days of age. Kirpnick-Sobol *et al.* (2006) reported that in embryos exposed to Cr III, significant increases in DNA deletions were seen at threefold lower chromium tissue concentrations than in embryos exposed to Cr VI. They concluded that, although only small amounts of Cr III were absorbed, Cr III was highly effective at inducing DNA damage.

Study Rationale

The California Congressional Delegation, California Environmental Protection Agency, and the California Department of Health Services nominated Cr VI for toxicity and carcinogenicity testing because of concerns over its presence in drinking water source supplies, its potential health effects, including carcinogenicity, and the lack of adequate carcinogenicity studies of ingested Cr VI. The results of 3-month toxicity studies of Cr VI administered in drinking water to F344/N rats and B6C3F1, BALB/c, and *am3*-C57BL/6 mice as sodium dichromate dihydrate have been published (NTP, 2007a). Hexavalent chromium is a human carcinogen by inhalation exposure, but available data are inadequate to evaluate its carcinogenic potential when ingested in drinking water. This Technical Report summarizes the results of 2-year toxicology and carcinogenesis drinking water studies conducted in male and female F344/N rats and B6C3F1 mice.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SODIUM DICHROMATE DIHYDRATE

Sodium dichromate dihydrate was obtained from Aldrich Chemical Company (Milwaukee, WI) in two lots. The two lots were combined at the analytical chemistry laboratory, Battelle Memorial Institute (Columbus, OH), and assigned a new lot number (062001) for use in the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, the study laboratory (Southern Research Institute, Birmingham, AL), Galbraith Laboratories, Inc. (Knoxville, TN), and Elemental Analysis Corp. (Lexington, KY) (Appendix F). Reports on analyses performed in support of the sodium dichromate dihydrate studies are on file at the National Institute of Environmental Health Sciences.

Lot 062001, an orange crystalline solid, was identified as sodium dichromate dihydrate by the analytical chemistry laboratory using X-ray diffraction, by the analytical chemistry laboratory and by Galbraith Laboratories, Inc., using elemental analysis by inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and by Elemental Analysis Corp. using proton-induced X-ray emission spectroscopy (PIXE). Elemental analyses for chromium and sodium by ICP-AES were in agreement with the theoretical values for sodium dichromate dihydrate, and PIXE indicated the absence of significant metallic impurities.

The moisture content of lot 062001 was determined by Galbraith Laboratories, Inc., using Karl Fischer titration. The purity of lot 062001 was determined by the analytical chemistry laboratory using differential scanning calorimetry (DSC), titration of the dichromate ion with sodium thiosulfate and potassium ferrocyanide, and speciation of the chromium ions using liquid chromatography-inductively coupled plasma-mass spectrometry (LC-ICP-MS) and by the study laboratory using potentiometric titration with sodium thiosulfate. Karl Fischer titration indicated a water content of 11.62%, which is in agreement with the theoretical value of 12.09%. DSC indicated a purity of 99.73% ± 0.15%. Titration with sodium thiosulfate by the analytical chemistry laboratory indicated a purity of 99.7% ± 0.1%. Titration with sodium thiosulfate by the study laboratory indicated purities of 101% and 102% relative to a frozen reference standard of the same lot. Titration with potassium ferrocyanide indicated a purity of 103.1% ± 0.2%. LC-ICP-MS indicated that the concentration of Cr III, if present, was less than 0.1%. The overall purity of lot 062001 was determined to be greater than 99.7%.

To ensure stability, the bulk chemical was stored at room temperature, protected from light in amber glass bottles.
Periodic reanalyses of the bulk chemical were performed by the study laboratory using potentiometric titration as described for the purity assays; no degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared approximately every 2 weeks by mixing sodium dichromate dihydrate with tap water (Table F1). Formulations were stored in NALGENE® containers at room temperature for up to 42 days.

Stability studies of a 41.8 µg/mL dose formulation were performed by the analytical chemistry laboratory using ion chromatography. Stability was confirmed for at least 42 days for dose formulations stored in sealed NALGENE® containers, protected from light, at temperatures up to room temperature and for at least 7 days when stored in drinking water bottles under simulated animal room conditions.

Periodic analyses of the dose formulations of sodium dichromate dihydrate were conducted by the study laboratory using ultraviolet/visible/near infrared spectroscopy (350 to 390 nm). The dose formulations were analyzed approximately every 10 weeks (Table F2). Of the dose formulations analyzed, all 44 for rats and all 84 for mice were within 10% of the target concentra-

tions. Animal room samples and unused carboy storage samples of these dose formulations were also analyzed; all 16 animal room samples for rats and 34 of 35 animal room samples for mice were within 10% of the target concentrations. Fourteen of 16 carboy samples for rats and 33 of 35 carboy samples for mice were within 10% of the target concentrations.

The sodium dichromate dihydrate dosed water used in these studies was slightly acidic. Based on an equilibrium constant of 50, dichromate predominates at the highest exposure concentration and the chromate:dichromate ratio approaches 1 at the lowest exposure concentration. These ratios would be obtained when the starting material was a chromate or dichromate salt.

Exposure Concentration Rationale for Rats and Mice

The 2-year studies were designed after an NTP public meeting on hexavalent chromium held on July 24, 2002, at the National Institute of Environmental Health Sciences in Research Triangle Park, NC, to consider the results of the prechronic studies and recommendations from the panel of scientific experts convened at this meeting (NTP, 2006). Exposure concentrations were selected based on these public discussions and careful review of the data from the 3-month toxicity studies. Based on source water concentrations, an additional low exposure concentration group was added to the 2-year studies to provide a concentration that was closer to concentrations to which humans might be exposed through the drinking water. A wider spacing of the exposure concentrations was also recommended to extend the dose-response curve. The highest exposure concentration in rats and mice was limited by toxicity observed in the 3-month studies. In the 3-month studies, reductions in body weight and water consumption and increased incidences of ulcers in the glandular stomach were observed in male and female rats exposed to 1,000 mg sodium dichromate dihydrate/L. Based on these considerations, the exposure concentrations of total chromium recommended were 0, 5, 20, 60, or 180 mg/L for male and female rats. These exposure concentrations are equivalent to 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate. In mice, significant reductions in body weight and water consumption were observed in males exposed to 500 or 1,000 mg/L and females exposed to 1,000 mg/L. Based on these considerations, the exposure concentrations of total chromium recommended were 0, 5, 10, 30, or 90 mg/L for male mice and 0, 5, 20, 60, or 180 mg/L for female mice. These exposure concentrations are equivalent to 0, 14.3, 28.6, 85.7, or 257.4 mg/L and 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate for males and females, respectively.

2-Year Studies

Study Design

Groups of 50 male and 50 female core study rats and mice were exposed to sodium dichromate dihydrate in drinking water at concentrations of 0, 14.3, 57.3, 172, or 516 mg/L (rats and female mice) or 0, 14.3, 28.6, 85.7, or 257.4 mg/L (male mice) for 105 to 106 weeks. Groups of 40 male special study rats and 40 female special study mice were exposed to the same concentrations for up to 53 weeks, and these animals were used for clinical pathology (Appendix E) and for tissue distribution (Appendix J) studies. Groups of 12 male clinical pathology rats and 16 female clinical pathology mice were exposed to the same concentrations for 22 days.

Source and Specification of Animals

Male and female F344/N rats and B6C3F1 mice were obtained from Taconic Farms, Inc. (Germantown, NY), for use in the 2-year studies. Core study rats and mice were quarantined for 14 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 to 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

Core study rats were housed three (males) or five (females) per cage, and core study mice were housed one (males) or five (females) per cage. Feed and water were available *ad libitum*. Water consumption was measured weekly for the first 13 weeks and then every 4 weeks for a 7-day period each time. Cages were changed once (male mice) or twice weekly, and cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix H.

Clinical Examinations and Pathology

All animals were observed twice daily and were weighed initially, weekly for the first 13 weeks, at 4-week intervals thereafter, and at the end of the studies. Clinical findings were recorded at 4-week intervals beginning at week 5.

Hematology and clinical chemistry (rats only) evaluations were performed on up to 10 clinical pathology rats on day 4, clinical pathology rats and mice on day 22, and special study rats and mice at 3, 6, and 12 months. At these time points, rats and mice were anesthetized with CO_2/O_2, and blood was taken from the retroorbital sinus. Clinical pathology animals were removed from the study after blood collection on day 22. Blood samples for hematology analyses were placed in tubes containing potassium EDTA as the anticoagulant; blood samples for the clinical chemistry analyses were placed in tubes not containing an anticoagulant, allowed to clot at room temperature, and centrifuged, and the serum was separated. Slides for hematology were stained with a modified Wright's stain using an Ames HEMATEK® slide stainer (Miles Laboratory, Elkhart, IN), and hematology determinations including erythrocyte and leukocyte counts, hemoglobin concentration, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell concentration were performed on an ADVIA™ 120 automated hematology analyzer (Bayer, Inc., Tarrytown, NY) with reagents provided by Bayer, Fisher Scientific (Norcross, GA), or Sigma Diagnostics (St. Louis, MO). Nucleated erythrocyte counts were determined by blood smears stained with neutral Wright-Giemsa stain and microscopically examined. Reticulocyte counts were obtained through sphering of blood smears with a zwitterionic agent and stained with an Oxazine dye; blood smears stained with New Methylene Blue Stain (Accustain Reticulocyte Stain; Sigma Diagnostics) were examined microscopically for the determination of manual reticulocyte counts. Clinical chemistry measurements were performed on a Hitachi 911 random access automated chemistry analyzer (Boehringer Mannheim, Indianapolis, IN) using reagents from Roche Sigma Diagnostics, Trinity Biotech (Overland, MO), or Diagnostic Chemicals, Ltd. (Oxford, CT).

Complete necropsies and microscopic examinations were performed on all core study rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, trimmed and processed, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1. During the audit of the pathology specimens for the rat and mouse studies, the residual wet tissues of the gastrointestinal tract from male and female rats and mice from all groups were examined to ensure that the entire gastrointestinal tract was adequately opened. Any untrimmed potential lesions were collected for microscopic evaluation.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy; the slide and tissue counts were verified; and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides of all neoplasms and all potential target organs for all animals which included the glandular stomach, small intestine (duodenum, ileum, jejunum), large intestine (cecum, colon), liver, oral mucosa, and tongue of rats and the forestomach, glandular stomach, small intestine (duodenum, ileum, jejunum), and large intestine (cecum, colon) of mice. In addition, slides for all animals were reviewed for specific lesions in the bone marrow, kidney, pancreatic and mesenteric lymph nodes, and salivary glands of rats and the bone marrow, kidney, pancreatic and mesenteric lymph nodes, pancreas, spleen, thymus, and urinary bladder of mice.

The oral mucosa and tongue are not protocol-required tissues, and as such, only lesions that are observed grossly in these sites are routinely evaluated histologically. Because the gross lesions observed in the oral mucosa were diagnosed as neoplasms, the oral mucosa (present on slides of the three standard sections of the nasal cavity required to be evaluated for each study) from all male and female rats and mice in all exposure concentration groups was evaluated for neoplastic and nonneoplastic lesions by the quality assessment and Pathology Working Group (PWG) pathologists. Histologic sections of the tongue were prepared for all male and female rats and mice in all exposure concentration groups and were evaluated for neoplastic and nonneoplastic lesions.

The quality assessment report and the reviewed slides were submitted to the NTP PWG chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Study Laboratory
Southern Research Institute (Birmingham, AL)

Strain and Species
F344/N rats
B6C3F1 mice

Animal Source
Taconic Farms, Inc. (Germantown, NY)

Time Held Before Studies
14 days

Average Age When Studies Began
6 to 7 weeks

Date of First Exposure
Rats: October 2, 2002
Mice: September 4, 2002

Duration of Exposure
105 to 106 weeks

Date of Last Exposure
Rats: October 7, 2004
Mice: September 9, 2004

Necropsy Dates
Rats: September 29 to October 7, 2004
Mice: September 1 to 9, 2004

Average Age at Necropsy
110 to 112 weeks

Size of Study Groups
Core study: 50 males and 50 females
Clinical pathology study: 12 male rats and 16 female mice
Special study: 40 male rats and 40 female mice

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
Rats: 3 (males) or 5 (females)
Mice: 1 (males) or 5 (females)

Method of Animal Identification
Tail tattoo

Diet
Irradiated NTP-2000 wafers (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly

Water
Tap water (Birmingham municipal supply) via amber glass bottles (Wheaton Science Products, Millville, NJ) with Teflon®-lined plastic screw caps fitted with stainless steel, double-ball sipper tubes, available *ad libitum*, changed twice weekly

Cages
Solid-bottom polycarbonate (Lab Products, Maywood, NJ), changed once (male mice) or twice weekly

Bedding
Heat-treated, irradiated hardwood chips (P.J. Murphy Forest Products, Inc., Montville, NJ), changed once (male mice) or twice weekly

Rack Filters
Reemay® spun-bonded polyester (Andico, Birmingham, AL), changed every 2 weeks

Racks
Stainless steel (Lab Products, Maywood, NJ), changed and rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Exposure Concentrations
Rats: 0, 14.3, 57.3, 172, and 516 mg/L in drinking water, available *ad libitum*
Mice: 0, 14.3, 28.6, 85.7, and 257.4 mg/L (males) or 0, 14.3, 57.3, 172, and 516 mg/L (females) in drinking water, available *ad libitum*

Type and Frequency of Observation
Observed twice daily; core study animals were weighed initially, weekly for the first 13 weeks, at 4-week intervals thereafter, and at the end of the studies; clinical findings for core study animals were recorded at 4-week intervals beginning at week 5. Water consumption by core study animals was recorded weekly for the first 13 weeks and every 4 weeks thereafter with each water consumption measurement covering a 7-day period.

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
Necropsies were performed on all core study animals.

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Clinical Pathology
Blood was collected from the retroorbital sinus of clinical pathology male rats and female mice on days 4 (rats only) and 22 and from special study male rats and female mice at 3, 6, and 12 months for hematology and clinical chemistry (rats only).
Hematology: hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; erythrocyte and platelet morphology; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials
Clinical chemistry: urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrodrogenase, bile acids

Histopathology
Complete histopathology was performed on all core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, eye, gallbladder (mice only), Harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, tongue, trachea, urinary bladder, and uterus.

Chromium Tissue Distribution
On days 4 and 11 and at 6 and 12 months, 10 special study rats and 8 or 10 special study mice were removed from treatment; five rats and all mice were placed in metabolism cages for 48 hours for urine and feces collection. Urine volume, feces weight, and urine creatinine concentration were determined. All special study rats and mice were anesthetized with CO_2/O_2, and following blood collection for clinical pathology, the liver, kidneys, and stomach (glandular and nonglandular) were collected. Urine, feces, and tissues were frozen until further analysis.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B4, C1, C4, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2, B2, C2, and D2) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., Harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A2, B2, C2, and D2 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk.

For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F1 mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

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

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology and clinical chemistry data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) (as modified by Williams, 1986) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1957) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The NTP historical database contains all studies that use the NTP-2000 diet with histopathology findings completed within the most recent 5-year period. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison, including the present study.

Quality Assurance Methods

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

RESULTS

RATS

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 1). Survival of exposed groups was similar to that of the control groups.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of the 14.3, 57.3, and 172 mg/L groups of male and female rats were generally similar to those of the control groups throughout the study (Tables 3 and 4; Figure 2). Mean body weights of 516 mg/L males and females were less than those of controls throughout the study and by the end of the study were 88% and 89% that of the respective controls. The lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption rather than direct toxic effects of sodium dichromate dihydrate exposure. Water consumption by 172 and 516 mg/L rats was less than that by the controls throughout the study (Tables G1 and G2). Decreases were evident from the first week of the study and continued until terminal sacrifice. During the second year of the study, the average water consumption was reduced by 15% and 22% and by 15% and 27% that of the controls in the 172 and 516 mg/L male and female rats, respectively. Drinking water concentrations of 14.3, 57.3, 172, or 516 mg/L resulted in average daily doses of approximately 0.6, 2.2, 6, or 17 mg sodium dichromate dihydrate/kg body weight for male rats and 0.7, 2.7, 7, or 20 mg/kg for female rats. No clinical findings were attributed to sodium dichromate dihydrate exposure.

TABLE 2
Survival of Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Animals initially in study	50	50	50	50	50
Missing[a]	0	0	1	0	1
Moribund	16	15	16	9	16
Natural deaths	6	5	3	5	4
Animals surviving to study termination	28	30	30	36	29
Percent probability of survival at end of study[b]	56	60	61	72	59
Mean survival (days)[c]	695	670	672	692	694
Survival analysis[d]	P=0.904N	P=1.000N	P=1.000N	P=0.221N	P=1.000N
Female					
Animals initially in study	50	50	50	50	50
Moribund	12	15	9	10	18
Natural deaths	5	3	9	4	1
Animals surviving to study termination	33[e]	32	32	36	31
Percent probability of survival at end of study	66	64	64	72	62
Mean survival (days)	696	691	694	686	685
Survival analysis	P=0.748	P=0.959	P=0.965	P=0.806N	P=0.745

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

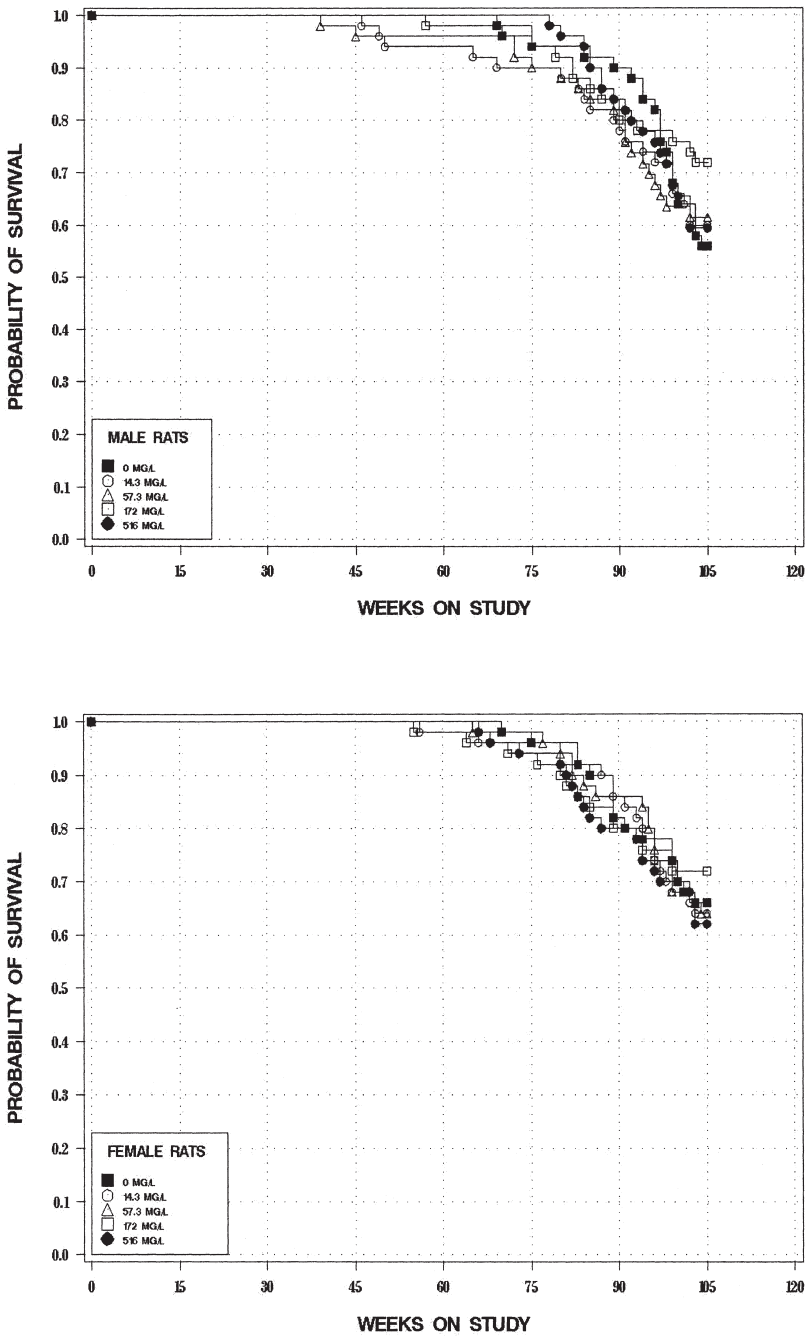


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	118	50	117	99	50	117	99	50
8	151	50	149	99	50	146	97	50
15	185	50	183	99	50	181	98	50
22	218	50	215	99	50	213	98	50
29	243	50	240	99	50	239	99	50
36	261	50	257	99	50	257	99	50
43	275	50	271	99	50	272	99	50
50	289	50	286	99	50	285	99	50
57	305	50	301	99	50	302	99	50
64	317	50	312	99	50	313	99	50
71	334	50	329	98	50	331	99	50
78	345	50	340	99	50	339	98	50
85	351	50	345	98	50	348	99	50
113	387	50	381	98	50	383	99	50
141	410	50	404	99	50	407	99	50
169	434	50	427	98	50	431	99	50
197	451	50	443	98	50	448	99	50
225	468	50	458	98	50	464	99	50
253	480	50	471	98	50	477	99	50
281	488	50	478	98	50	483	99	49
309	490	50	485	99	50	488	100	49
337	501	50	495	99	48	497	99	48
365	511	50	502	98	47	505	99	48
393	515	50	507	98	47	512	99	48
421	523	50	515	98	47	519	99	48
449	524	50	515	98	47	519	99	48
477	525	50	516	98	45	518	99	48
505	525	48	517	98	45	520	99	46
533	530	47	519	98	45	525	99	45
561	532	47	518	97	44	525	99	44
589	531	46	515	97	42	522	98	43
617	529	45	519	98	40	519	98	40
645	526	44	517	98	38	520	99	36
673	513	41	515	100	36	517	101	32
701	515	32	503	98	33	514	100	31
Mean for weeks								
1-13	261		257	99		257	99	
14-52	457		449	98		453	99	
53-101	523		514	98		518	99	

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	172 mg/L Av. Wt. (g)	172 mg/L Wt. (% of controls)	172 mg/L No. of Survivors	516 mg/L Av. Wt. (g)	516 mg/L Wt. (% of controls)	516 mg/L No. of Survivors
1	117	99	50	118	100	50
8	147	97	50	143	95	50
15	180	97	50	173	93	50
22	210	97	50	201	93	50
29	235	97	50	225	93	50
36	254	97	50	243	93	50
43	267	97	50	257	93	50
50	279	96	50	270	93	50
57	295	96	50	285	93	50
64	304	96	50	295	93	50
71	321	96	50	311	93	50
78	330	96	50	320	93	50
85	338	96	50	324	92	50
113	373	96	50	363	94	50
141	395	96	50	386	94	50
169	418	96	50	407	94	50
197	437	97	50	424	94	50
225	449	96	50	437	94	50
253	462	96	50	447	93	50
281	469	96	50	454	93	50
309	477	97	50	461	94	50
337	486	97	50	468	94	50
365	490	96	50	475	93	50
393	496	96	50	479	93	50
421	503	96	49	485	93	50
449	504	96	49	484	92	50
477	503	96	49	484	92	50
505	501	96	49	483	92	50
533	508	96	47	487	92	50
561	507	95	46	483	91	48
589	506	95	44	473	89	47
617	502	95	42	480	91	41
645	501	95	39	474	90	39
673	500	97	39	462	90	36
701	500	97	38	455	88	32
Mean for weeks						
1-13	252	97		243	94	
14-52	441	96		427	94	
53-101	502	96		477	91	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	100	50	99	99	50	100	99	50
9	122	50	120	99	50	121	99	50
16	135	50	132	98	50	134	99	50
23	150	50	146	97	50	147	98	50
30	157	50	154	98	50	154	98	50
37	164	50	161	98	50	162	98	50
44	170	50	168	99	50	167	98	50
51	175	50	172	98	50	172	98	50
58	180	50	178	99	50	177	98	50
65	183	50	180	99	50	180	98	50
72	188	50	184	98	50	185	98	50
79	193	50	189	98	50	188	97	50
86	198	50	193	97	50	192	97	50
114	208	50	203	97	50	202	97	50
142	217	50	211	97	50	209	96	50
170	229	50	223	98	50	221	97	50
198	237	50	229	97	50	229	97	50
226	246	50	239	97	50	237	96	50
254	255	50	248	97	50	246	97	50
282	263	50	255	97	50	253	96	50
310	272	50	261	96	50	262	96	50
338	281	50	271	96	50	271	96	50
366	289	50	279	97	50	278	96	50
394	297	50	288	97	49	287	97	50
422	309	50	297	96	49	297	96	50
450	314	50	302	96	49	304	97	50
478	317	50	307	97	48	310	98	49
506	323	49	312	97	48	315	98	49
534	332	48	323	97	48	322	97	48
562	337	48	328	98	46	325	97	47
590	341	46	332	97	46	333	98	44
618	336	42	332	99	43	333	99	43
646	348	40	336	96	41	340	98	43
674	350	39	339	97	37	346	99	38
702	351	35	338	96	34	346	98	34
Mean for weeks								
1-13	163		160	98		160	98	
14-52	245		238	97		237	96	
53-101	326		316	97		318	98	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	172 mg/L			516 mg/L		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	99	99	50	99	98	50
9	119	98	50	115	94	50
16	131	97	50	129	95	50
23	145	97	50	144	96	50
30	153	97	50	152	97	50
37	161	98	50	159	97	50
44	166	98	50	165	97	50
51	171	97	50	170	97	50
58	175	97	50	175	97	50
65	178	97	50	178	97	50
72	183	98	50	182	97	50
79	186	97	50	186	96	50
86	192	97	50	190	96	50
114	201	97	50	199	96	50
142	206	95	50	207	95	50
170	218	95	50	215	94	50
198	226	95	50	222	94	50
226	235	96	50	230	94	50
254	242	95	50	237	93	50
282	248	94	50	242	92	50
310	256	94	50	248	91	50
338	265	94	50	254	90	50
366	272	94	50	263	91	50
394	279	94	49	268	90	50
422	290	94	49	275	89	50
450	296	94	48	281	89	50
478	302	95	48	284	90	48
506	308	95	47	290	90	47
534	318	96	46	298	90	47
562	319	95	45	300	89	46
590	325	95	42	307	90	42
618	326	97	40	314	93	40
646	333	96	39	315	90	40
674	337	96	37	318	91	36
702	340	97	36	312	89	35
Mean for weeks						
1-13	158	97		157	96	
14-52	233	95		228	93	
53-101	311	95		294	90	

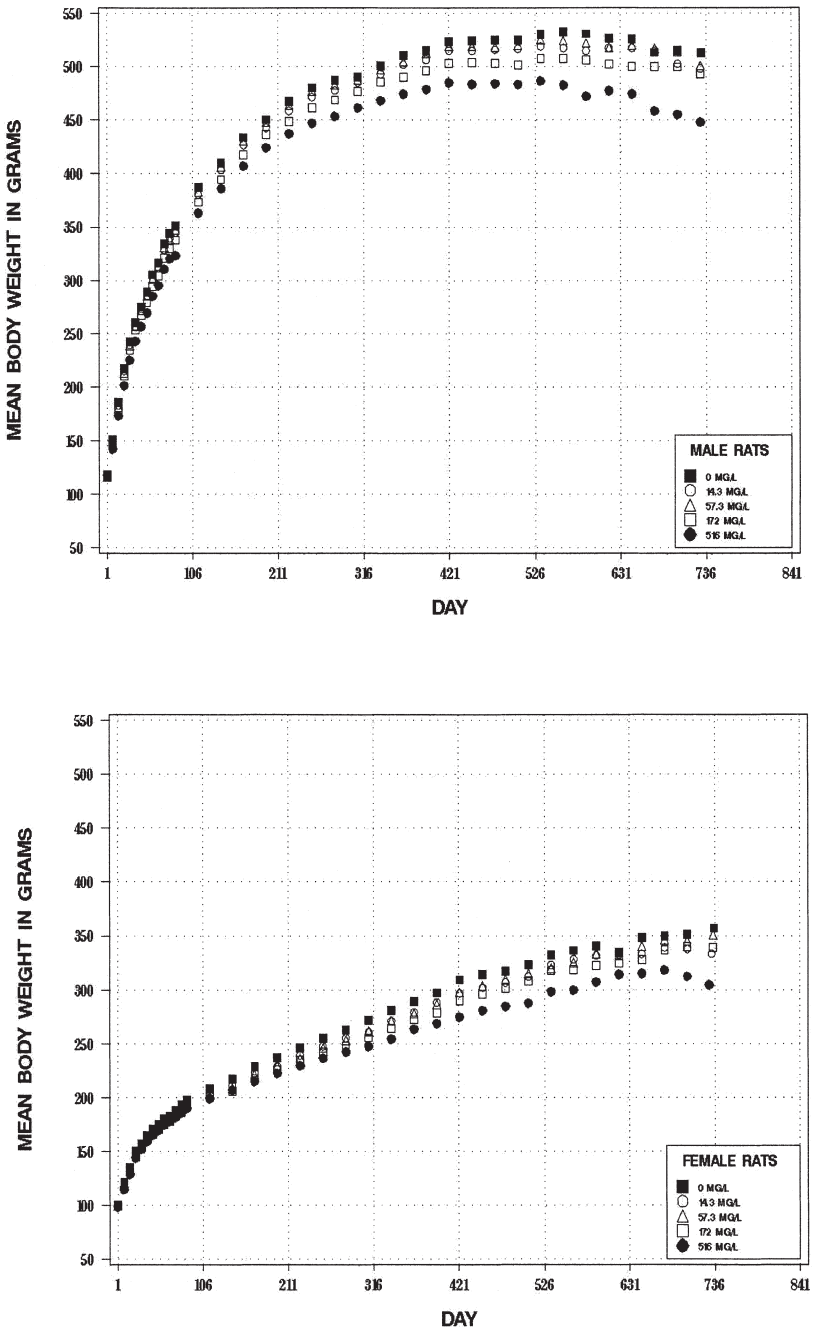


FIGURE 2
Growth Curves for Male and Female Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

Hematology and Clinical Chemistry

The hematology and clinical chemistry data for male rats are listed in Tables 5 and E1. An exposure concentration-related erythrocyte microcytosis, evidenced by decreased mean cell volumes, occurred on day 4 and persisted throughout the study in the 172 and 516 mg/L groups; the 57.3 mg/L group demonstrated minor changes on day 22 and at months 3 and 6. In the 516 mg/L animals, the severity of the microcytosis peaked with an approximately 20% to 25% decrease in red cell size on day 22 and at month 3. The severity of the microcytosis ameliorated with time. For example, by 12 months, the red cells of the 516 mg/L animals were only 5% smaller than those of the controls. Changes in the mean cell hemoglobin value mimicked the alterations in mean cell volume and were a reflection of the smaller red cells. Mean cell hemoglobin concentration demonstrated small, exposure concentration-related decreases (less than or equal to 10%) in the 172 and 516 mg/L animals. The mean cell hemoglobin concentration decreases were most severe on day 22 or at month 3; they ameliorated with time.

An exposure-related anemia, evidenced by decreases in hematocrit (instrument-derived), packed cell volume (spun microhematocrit), hemoglobin, and erythrocyte count values, developed by day 22 and affected the 57.3, 172, and 516 mg/L groups. The anemia was most severe on day 22 (an approximate 30% decrease in the 516 mg/L group) but resolved with time. In fact, at 3 months, erythrocyte counts were increased, in contrast to the lower hematocrit and hemoglobin values in the 516 mg/L group; the erythrocyte counts remained slightly elevated (less than 10%) in the higher-exposed animals out to the 12-month time point. The increased numbers of nucleated erythrocytes and/or reticulocytes in the 516 mg/L animals on day 22 and at month 3 were indicative of an erythropoietic response. Microscopic evaluation of the blood smears demonstrated increased poikilocytes, erythrocyte fragments/schizocytes, keratocytes, erythrocyte hypochromia, and microcytes that suggested increased erythrocyte injury or turnover. These changes were most prominent in the higher-exposed animals on day 22 and at month 3. Taken together, it appears that the erythropoietic tissues were able to respond to the anemia (also evidenced by slightly increased incidences of bone marrow hyperplasia in the core study male rats (0 mg/L, 4/50; 14.3 mg/L, 12/50; 57.3 mg/L, 7/49; 172 mg/L, 7/50; 516 mg/L, 6/49; Table A4), but there was some ineffective erythropoiesis resulting in production of increased numbers of smaller erythrocytes. This effect was not observed at 6 or 12 months demonstrating that, with time, the animals adapted to exposure.

Increases in serum alanine aminotransferase activity occurred in the 57.3 mg/L or greater groups; however, serum sorbitol dehydrogenase activities and bile acid concentrations were unaffected (Table E1). The severity of the serum alanine aminotransferase activity increases peaked at 3 months (e.g., greater than a twofold increase in the 516 mg/L group), stabilized, and remained elevated at this level to the 12-month time point. While there was an indication of a chronic inflammatory process of minimal severity in the liver, the lack of corroborating evidence in other markers of liver injury suggests that the alanine aminotransferase increases may have been related to enzyme induction in the liver instead of increased hepatocellular membrane leakage.

TABLE 5
Selected Hematology Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 4	9	10	9	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	8	10
Hematocrit (auto) (%)					
Day 4	37.5 ± 0.5	37.7 ± 0.5	36.4 ± 0.8	35.8 ± 0.7	37.0 ± 0.6
Day 22	46.5 ± 0.9	45.3 ± 0.5	44.2 ± 0.7	38.4 ± 0.8**	28.0 ± 0.6**
Month 3	45.1 ± 0.3	44.6 ± 0.4	44.7 ± 0.5	44.6 ± 0.5	43.0 ± 0.5**
Month 6	46.5 ± 0.3	46.7 ± 0.5	46.3 ± 0.5	46.5 ± 0.4	46.0 ± 0.3
Month 12	48.8 ± 0.6	48.0 ± 0.4	48.8 ± 0.7	49.3 ± 0.5	48.6 ± 0.4
Hematocrit (spun) (%)					
Day 4	38.2 ± 0.5[b]	38.4 ± 0.6	36.7 ± 0.9	36.4 ± 0.6	37.3 ± 0.6
Day 22	46.0 ± 1.1	44.4 ± 0.4	43.2 ± 0.6*	38.7 ± 0.6**	33.5 ± 0.8**
Month 3	45.3 ± 0.4	44.5 ± 0.3	44.5 ± 0.4	44.1 ± 0.5	41.0 ± 0.5**
Month 6	45.9 ± 0.4	45.7 ± 0.5	45.5 ± 0.4	45.5 ± 0.5	45.0 ± 0.3
Month 12	47.6 ± 0.5	46.6 ± 0.4	47.4 ± 0.5	47.7 ± 0.4	47.3 ± 0.4
Hemoglobin (g/dL)					
Day 4	12.9 ± 0.2	13.0 ± 0.2	12.5 ± 0.3	12.3 ± 0.2	12.8 ± 0.2
Day 22	15.5 ± 0.3	15.1 ± 0.2	14.2 ± 0.2**	12.0 ± 0.3**	10.1 ± 0.2**
Month 3	15.1 ± 0.1	14.9 ± 0.1	14.9 ± 0.2	14.6 ± 0.2*	12.9 ± 0.2**
Month 6	15.2 ± 0.1	15.2 ± 0.2	15.0 ± 0.2	14.9 ± 0.1	14.5 ± 0.1**
Month 12	15.8 ± 0.2	15.4 ± 0.2	15.6 ± 0.2	15.6 ± 0.2	15.3 ± 0.1*
Erythrocytes (10^6/µL)					
Day 4	6.75 ± 0.11	6.80 ± 0.10	6.67 ± 0.17	6.73 ± 0.11	6.98 ± 0.12
Day 22	7.80 ± 0.13	7.74 ± 0.15	8.06 ± 0.16	8.10 ± 0.14	6.21 ± 0.13**
Month 3	9.28 ± 0.05	9.24 ± 0.06	9.46 ± 0.11	9.75 ± 0.11**	10.93 ± 0.16**
Month 6	9.34 ± 0.06	9.43 ± 0.08	9.54 ± 0.11	9.71 ± 0.08**	10.15 ± 0.13**
Month 12	9.27 ± 0.10	9.17 ± 0.07	9.40 ± 0.12	9.61 ± 0.11	9.74 ± 0.08**
Reticulocytes (auto) (10^6/µL)					
Day 4	0.62 ± 0.04	0.56 ± 0.04	0.50 ± 0.04	0.24 ± 0.02**	0.19 ± 0.02**
Day 22	0.38 ± 0.03	0.34 ± 0.02	0.38 ± 0.03	0.43 ± 0.04	0.63 ± 0.07**
Month 3	0.23 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.30 ± 0.01**
Month 6	0.24 ± 0.00	0.22 ± 0.01	0.22 ± 0.01	0.24 ± 0.01	0.24 ± 0.01
Month 12	0.23 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.26 ± 0.02	0.23 ± 0.01
Reticulocytes (manual) (10^6/µL)					
Day 4	0.30 ± 0.06	0.29 ± 0.03	0.29 ± 0.06	0.30 ± 0.03	0.27 ± 0.02
Day 22	0.32 ± 0.04	0.27 ± 0.03	0.30 ± 0.03	0.41 ± 0.05	0.52 ± 0.04**
Month 3	0.12 ± 0.02	0.14 ± 0.02	0.10 ± 0.02	0.11 ± 0.03	0.13 ± 0.02
Month 12	0.19 ± 0.02	0.18 ± 0.01	0.21 ± 0.02	022 ± 0.03	0.17 ± 0.01
Nucleated erythrocytes (10^3/µL)					
Day 4	0.50 ± 0.17[b]	0.60 ± 0.22	0.20 ± 0.13[b]	0.50 ± 0.17	0.10 ± 0.10
Day 22	0.20 ± 0.13	0.20 ± 0.13	0.30 ± 0.15	0.30 ± 0.21	1.40 ± 0.22**
Month 3	0.20 ± 0.13	0.40 ± 0.22	0.30 ± 0.21	0.20 ± 0.13	0.00 ± 0.00
Month 6	0.30 ± 0.15	0.10 ± 0.10	0.20 ± 0.13	0.10 ± 0.10	0.40 ± 0.22
Month 12	0.30 ± 0.21	0.30 ± 0.21	0.10 ± 0.10	0.38 ± 0.26	0.10 ± 0.10
Mean cell volume (fL)					
Day 4	55.6 ± 0.3	55.5 ± 0.3	54.6 ± 0.3	53.3 ± 0.1**	53.0 ± 0.2**
Day 22	59.5 ± 0.4	58.6 ± 0.5	54.9 ± 0.5**	47.4 ± 0.4**	45.0 ± 0.7**
Month 3	48.6 ± 0.2	48.3 ± 0.2	47.3 ± 0.2**	45.7 ± 0.2**	39.2 ± 0.6**
Month 6	49.8 ± 0.1	49.5 ± 0.1	48.6 ± 0.1**	47.8 ± 0.2**	45.4 ± 0.5**
Month 12	52.6 ± 0.2	52.4 ± 0.2	51.9 ± 0.3	51.4 ± 0.3**	49.9 ± 0.2**

TABLE 5
Selected Hematology Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 4	9	10	9	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	8	10
Mean cell hemoglobin (pg)					
Day 4	19.1 ± 0.1	19.1 ± 0.1	18.7 ± 0.1*	18.3 ± 0.1**	18.4 ± 0.1**
Day 22	19.8 ± 0.1	19.5 ± 0.2	17.7 ± 0.2**	14.8 ± 0.2**	16.3 ± 0.5**
Month 3	16.2 ± 0.1	16.2 ± 0.1	15.7 ± 0.0**	15.0 ± 0.1**	11.9 ± 0.3**
Month 6	16.3 ± 0.1	16.1 ± 0.1	15.7 ± 0.1**	15.3 ± 0.1**	14.3 ± 0.2**
Month 12	17.0 ± 0.1	16.8 ± 0.1	16.6 ± 0.1*	16.2 ± 0.1**	15.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)					
Day 4	34.4 ± 0.2	34.4 ± 0.2	34.3 ± 0.2	34.4 ± 0.2	34.7 ± 0.2
Day 22	33.3 ± 0.1	33.3 ± 0.1	32.2 ± 0.2	31.2 ± 0.2**	36.2 ± 0.8
Month 3	33.4 ± 0.1	33.5 ± 0.2	33.2 ± 0.1	32.7 ± 0.1**	30.2 ± 0.3**
Month 6	32.7 ± 0.1	32.5 ± 0.1	32.3 ± 0.1*	32.1 ± 0.1**	31.6 ± 0.2**
Month 12	32.3 ± 0.2	32.1 ± 0.3	32.0 ± 0.2	31.6 ± 0.2*	31.5 ± 0.2*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=10

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms or nonneoplastic lesions of the oral cavity (oral mucosa and tongue), liver, small intestine (duodenum), mesenteric lymph node, pancreatic lymph node, salivary gland, pancreas, and adrenal medulla. Summaries of the incidences of neoplasms and nonneoplastic lesions, 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 Appendix A for male rats and Appendix B for female rats.

Oral Cavity (Oral Mucosa and Tongue): Exposure to sodium dichromate dihydrate resulted in the development of neoplasms of the squamous epithelium that lines the oral mucosa and tongue. The incidences of squamous cell carcinoma in the oral mucosa of 516 mg/L male and female rats were significantly greater than those in the controls (Tables 6, A2, and B2). None were seen in concurrent or historical controls for drinking water studies. Squamous cell carcinomas were also observed in the oral mucosa of two 172 mg/L female rats and exceeded the historical control ranges for drinking water studies and for all routes of administration. One squamous cell carcinoma of the tongue occurred in a 14.3 mg/L male and one in a 172 mg/L female. A squamous cell papilloma of the oral mucosa occurred in one 516 mg/L male, and a squamous cell papilloma of the tongue occurred in one 516 mg/L male. One control and one 14.3 mg/L female had squamous cell papillomas of the tongue. The incidences of squamous cell papilloma or squamous cell carcinoma (combined) of the oral mucosa or tongue of 516 mg/L male and female rats were significantly greater than those in the controls (Table 6).

Microscopically, the squamous cell carcinomas of the oral mucosa were highly invasive, irregular masses. Typically, they appeared to originate in the oral mucosa of the palate adjacent to the upper molar teeth; invaded the tongue, Harderian gland, and the soft tissues surrounding the nose in some animals; and penetrated the maxilla and invaded the brain in one case. Carcinomas consisted of a mixture of variably sized islands and short, irregular cords of relatively welldifferentiated stratified squamous epithelium, surrounded by moderate amounts of dense fibrous connective tissue stroma (Plates 1 and 2). Frequently, the epithelium formed cyst-like structures filled with keratin (keratin pearls). The squamous cell papillomas of the oral mucosa and tongue were exophytic masses that projected from the mucosa and consisted of irregular papillary proliferations of mature squamous epithelium supported by a core of fibrovascular stroma. In the tongue, squamous cell carcinoma was diagnosed when the stroma of these papillary masses had evidence of invasion in the form of irregular foci of dysplastic epithelium (Plates 3 and 4).

TABLE 6
Incidences of Neoplasms of the Oral Cavity in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Male					
Number Necropsied	50	50	49	50	49
Oral Mucosa					
Squamous Cell Papilloma[a]	0	0	0	0	1
Squamous Cell Carcinoma[b]					
Overall Rate[c]	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	6/49 (12%)
Adjusted Rate[d]	0.0%	0.0%	0.0%	0.0%	13.6%
Terminal Rate[e]	0/28 (0%)	0/30 (0%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First Incidence (days)	—[g]	—	—	—	543
Poly-3 Test[f]	P<0.001	—[h]	—	—	P=0.015
Tongue					
Squamous Cell Papilloma	0	0	0	0	1
Squamous Cell Carcinoma	0	1	0	0	0
Oral Mucosa or Tongue					
Squamous Cell Papilloma or Squamous Cell Carcinoma[i]					
Overall Rate	0/50 (0%)	1/50 (2%)	0/49 (0%)	0/50 (0%)	7/49 (14%)
Adjusted Rate	0.0%	2.4%	0.0%	0.0%	15.7%
Terminal Rate	0/28 (0%)	1/30 (3%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First Incidence (days)	—	729 (T)	—	—	543
Poly-3 Test	P<0.001	P=0.487	—	—	P=0.007
Female					
Number Necropsied	50	50	50	50	50
Oral Mucosa					
Squamous Cell Carcinoma[j]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	11/50 (22%)
Adjusted Rate	0.0%	0.0%	0.0%	4.6%	23.9%
Terminal Rate	0/33 (0%)	0/32 (0%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First Incidence (days)	—	—	—	646	506
Poly-3 Test	P<0.001	—	—	P=0.233	P<0.001
Tongue					
Squamous Cell Papilloma	1	1	0	0	0
Squamous Cell Carcinoma	0	0	0	1	0

TABLE 6
Incidences of Neoplasms of the Oral Cavity in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female (continued)					
Oral Mucosa or Tongue					
Squamous Cell Papilloma or Squamous Cell Carcinoma[k]					
Overall Rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	11/50 (22%)
Adjusted Rate	2.2%	2.3%	0.0%	4.6%	23.9%
Terminal Rate	0/33 (0%)	1/32 (3%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First Incidence (days)	618	729 (T)	—	646	506
Poly-3 Test	P<0.001	P=0.756	P=0.503N	P=0.491	P=0.002

(T) Terminal sacrifice
[a] Number of animals with neoplasm
[b] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 0/350; all routes: 5/1,499 (0.3% ± 0.7%), range 0%-2%
[c] Number of animals with neoplasm per number of animals necropsied
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[g] Not applicable; no neoplasms in animal group
[h] Value of statistic cannot be computed.
[i] Historical incidence for drinking water studies: 1/300 (0.3% ± 0.8%), range 0%-2%; all routes: 10/1,449 (0.6% ± 0.8%), range 0%-2%
[j] Historical incidence for drinking water studies: 0/300; all routes: 5/1,400 (0.4% ± 0.8%), range 0%-2%
[k] Historical incidence for drinking water studies: 3/250 (1.2% ± 1.1%), range 0%-2%; all routes: 14/1,350 (1.1% ± 1.6%), range 0%-6%

Liver: The incidences of minimal to moderate histiocytic cellular infiltration in 516 mg/L males and in females exposed to 57.3 mg/L or greater were significantly greater than those in the controls (Tables 7, A4, and B4). The incidences of chronic inflammation in 172 mg/L males and all exposed groups of females were significantly increased. Chronic inflammation was generally of minimal to mild severity in most groups, including the controls, except 516 mg/L females in which there appeared to be a slight increase in the severity (mild to moderate). There were statistically significant, exposure concentration-related increases in the incidences of fatty change in female rats exposed to 57.3 mg/L or greater. The incidences of basophilic focus in males exposed to 57.3 or 172 mg/L were significantly increased. The incidence of clear cell focus in females exposed to 172 mg/L was significantly increased.

Histiocytic infiltrates were characterized by the presence of individual, small clusters and sometimes syncytia of histiocytes (macrophages) that were typically randomly scattered throughout the hepatic parenchyma but often occurred in increased numbers within the portal areas. The histiocytes were large (approximately 20 to 80 microns in diameter) and had abundant pale, lightly eosinophilic, faintly stippled cytoplasm and single, small, peripheral, dark basophilic nuclei (Plates 5 and 6). In minimally affected livers, the histiocytes often occurred singly, whereas in more severely affected livers, the histiocytes occurred as small clusters of a few cells. The biological significance of the histiocytic cellular infiltrates is unknown but may suggest phagocytosis of some insoluble chemical precipitate. Chronic inflammation consisted of small, randomly scattered aggregates of macrophages, lymphocytes, and neutrophils in variable numbers and in some cases were associated with the larger histiocytic infiltrates (Plate 7). Chronic inflammation is consistent with changes that are considered to be background or spontaneous lesions commonly observed in aged rats and appears to be exac-

TABLE 7
Incidences of Nonneoplastic Lesions of the Liver in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L		14.3 mg/L		57.3 mg/L		172 mg/L		516 mg/L	
Male										
Number Examined Microscopically	50		50		49		50		49	
Infiltration Cellular, Histiocyte[a]	1	(1.0)[b]	0		2	(1.0)	5	(1.4)	34**	(1.4)
Inflammation, Chronic	19	(1.1)	25	(1.2)	21	(1.3)	28*	(1.1)	26	(1.3)
Basophilic Focus	22		28		29*		32*		30	
Female										
Number Examined Microscopically	50		50		50		50		50	
Infiltration Cellular, Histiocyte	1	(1.0)	5	(1.0)	21**	(1.3)	42**	(2.0)	47**	(2.6)
Inflammation, Chronic	12	(1.3)	21*	(1.2)	28**	(1.3)	35**	(1.6)	39**	(2.1)
Fatty Change	3	(3.3)	7	(3.6)	10*	(2.5)	13**	(2.5)	16**	(2.8)
Clear Cell Focus	7		5		7		20**		7	

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

erbated by exposure. Fatty change consisted of scattered hepatocytes that contained one to several variably sized, discrete, clear, cytoplasmic vacuoles (fat droplets).

Small Intestine (Duodenum): The incidences of minimal to mild histiocytic cellular infiltration were significantly increased in males exposed to 57.3 mg/L or greater and in 172 and 516 mg/L females (Tables 8, A4, and B4). The infiltrating histiocytes were morphologically similar to those observed in the liver and occurred singly or as clusters of cells within the lamina propria at the tips of the duodenal villi (Plate 8).

Mesenteric Lymph Node: The incidences of histiocytic cellular infiltration in males exposed to 57.3 mg/L or greater and in 172 and 516 mg/L females were significantly increased compared to the controls (Tables 8, A4, and B4); there was a slight increase in the severity of infiltrates in 172 and 516 mg/L females with more animals in these groups having mild severity grades relative to the controls and the lower exposure concentration groups. The incidences of minimal lymph node hemorrhage in males exposed to 57.3 mg/L or greater and in 516 mg/L females were significantly increased and may have been caused by the histiocytic infiltrates in the lymph node. The histiocytic infiltrates were morphologically similar to those that occurred in the liver and duodenum. They formed numerous variably sized clusters randomly scattered within the cortex and/or medullary sinuses (Plates 9 and 10). Frequently, the clusters coalesced to form sheets that in some cases replaced much of the lymph node parenchyma.

Pancreatic Lymph Node: The incidences of histiocytic cellular infiltration were increased in the 516 mg/L males and in 57.3 mg/L or greater females with the incidence in 172 mg/L females being significantly greater than that in the controls (Tables 8, A4, and B4); the average severity of infiltration in 57.3 mg/L or greater females increased with increasing dose. Histiocytic infiltrates were morphologically similar to those that occurred in the liver, duodenum, and mesenteric lymph nodes.

Salivary Gland: The incidence of salivary gland atrophy was significantly increased in 172 mg/L females compared to that in the controls; in general, the average

TABLE 8
Incidences of Selected Nonneoplastic Lesions in Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L		14.3 mg/L		57.3 mg/L		172 mg/L		516 mg/L	
Male										
Small Intestine, Duodenum[a]	48		48		47		46		48	
Infiltration Cellular, Histiocyte[b]	0		0		6*	(1.2)[c]	36**	(1.1)	47**	(1.5)
Lymph Node, Mesenteric	49		50		49		50		49	
Infiltration Cellular, Histiocyte	13	(2.0)	11	(1.5)	30**	(1.9)	39**	(2.1)	41**	(2.1)
Hemorrhage	2	(1.5)	7	(1.1)	9*	(1.3)	8*	(1.1)	17**	(1.3)
Lymph Node, Pancreatic	32		34		34		36		33	
Infiltration Cellular, Histiocyte	17	(2.0)	22	(1.6)	17	(2.0)	17	(2.1)	25	(2.1)
Female										
Small Intestine, Duodenum	46		49		48		46		50	
Infiltration Cellular, Histiocyte	0		0		1	(1.0)	30**	(1.0)	47**	(1.2)
Lymph Node, Mesenteric	50		50		50		50		50	
Infiltration Cellular, Histiocyte	21	(1.7)	18	(1.4)	27	(1.5)	36**	(2.0)	42**	(2.4)
Hemorrhage	11	(1.1)	13	(1.3)	16	(1.3)	14	(1.1)	21*	(1.3)
Lymph Node, Pancreatic	29		36		30		34		33	
Infiltration Cellular, Histiocyte	17	(2.0)	20	(1.9)	23	(2.6)	32**	(2.8)	27	(3.0)
Salivary Gland	50		50		50		50		50	
Atrophy	9	(1.3)	7	(1.4)	10	(1.2)	17*	(1.4)	17	(2.1)

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

severity was minimal in the controls and in the 14.3, 57.3, and 172 mg/L groups, but mild in the 516 mg/L group. Microscopically, atrophy occurred as single, focal lesions in the salivary glands. Minimal lesions consisted of small, poorly defined foci of atrophic acini, whereas mild lesions were larger, well-defined foci. The atrophic foci consisted of shrunken glandular acini lined by low cuboidal epithelial cells devoid of secretory material, accompanied by an increased prominence of the interstitial stroma and ducts, some of which were variably dilated (Plates 11 and 12). Atrophy is an age-related spontaneous change commonly observed in rats. The biological significance of the increases in female rats in this study is uncertain.

Other Findings: Exposure to sodium dichromate dihydrate resulted in statistically significant increased incidences of neoplasms in one or more exposed groups. In general, the increased incidences occurred in one sex, one or more exposed groups, and were not exposure concentration related. These lesions included pancreatic acinar adenoma in males (0 mg/L, 1/50; 14.3 mg/L, 2/50; 57.3 mg/L, 6/49; 172 mg/L, 2/50; 516 mg/L, 2/49; Table A2); benign pheochromocytoma of the adrenal medulla in males (6/49, 13/50, 14/49, 5/50, 4/49; Table A2); and mononuclear cell leukemia in females (8/50, 18/50, 13/50, 7/50, 11/50; Table B2). The relationship of these changes to exposure is uncertain.

MICE

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 9 and in the Kaplan-Meier survival curves (Figure 3). Survival of all exposed groups was similar to that of the control groups.

Body Weights, Water and Compound Consumption, and Clinical Findings

The mean body weights of 257.4 mg/L male mice were less than those of the controls from months 2 through 6 of the study but were only slightly less than the control group by the end of the study; mean body weights of 172 mg/L females were less than those of the controls from months 3 through 12 of the study; and mean body weights of 516 mg/L females were less than those of the controls from month 2 until the end of the study (Tables 10 and 11; Figure 4). By the end of the study, the mean body weight of 172 mg/L females was 8% less than that of the controls, and the mean body weight of 516 mg/L females was 15% less than that of the control group. The lower body weights were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption rather than direct toxic effects of sodium dichromate dihydrate exposure. Water consumption by 85.7 and 257.4 mg/L males and 172 and 516 mg/L females was less than that by the controls throughout the study (Tables G3 and G4). During the second year of the study, the average water consumption was reduced by 15% and 35% than that of the controls in 85.7 and 257.4 mg/L males, respectively, and by 25% and 32% than that of the controls in the 172 and 516 mg/L females, respectively. Drinking water concentrations of 14.3, 28.6, 85.7, or 257.4 mg/L for males and 14.3, 57.3, 172, or 516 mg/L for females resulted in average daily doses of approximately 1.1, 2.6, 7, or 17 mg sodium dichromate dihydrate/kg body weight for male mice and 1.1, 3.9, 9, or 25 mg/kg for female mice. No clinical findings were attributed to sodium dichromate dihydrate exposure.

TABLE 9
Survival of Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Animals initially in study	50	50	50	50	50
Moribund	7	5	5	4	3
Natural deaths	10	10	10	8	15
Animals surviving to study termination	33[a]	35	35	38	32[a]
Percent probability of survival at end of study[b]	66	70	70	76	64
Mean survival (days)[c]	700	694	682	708	689
Survival analysis[d]	P=0.724	P=0.949N	P=0.982N	P=0.387N	P=0.918
	0 mg/L	**14.3 mg/L**	**57.3 mg/L**	**172 mg/L**	**516 mg/L**
Female					
Animals initially in study	50	50	50	50	50
Moribund	5	0	2	2	3
Natural deaths	8	11	3	6	5
Animals surviving to study termination	37[e]	39[a]	45[a]	42[e]	42
Percent probability of survival at end of study	74	78	90	84	84
Mean survival (days)	696	705	714	709	709
Survival analysis	P=0.504N	P=0.780N	P=0.068N	P=0.333N	P=0.285N

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

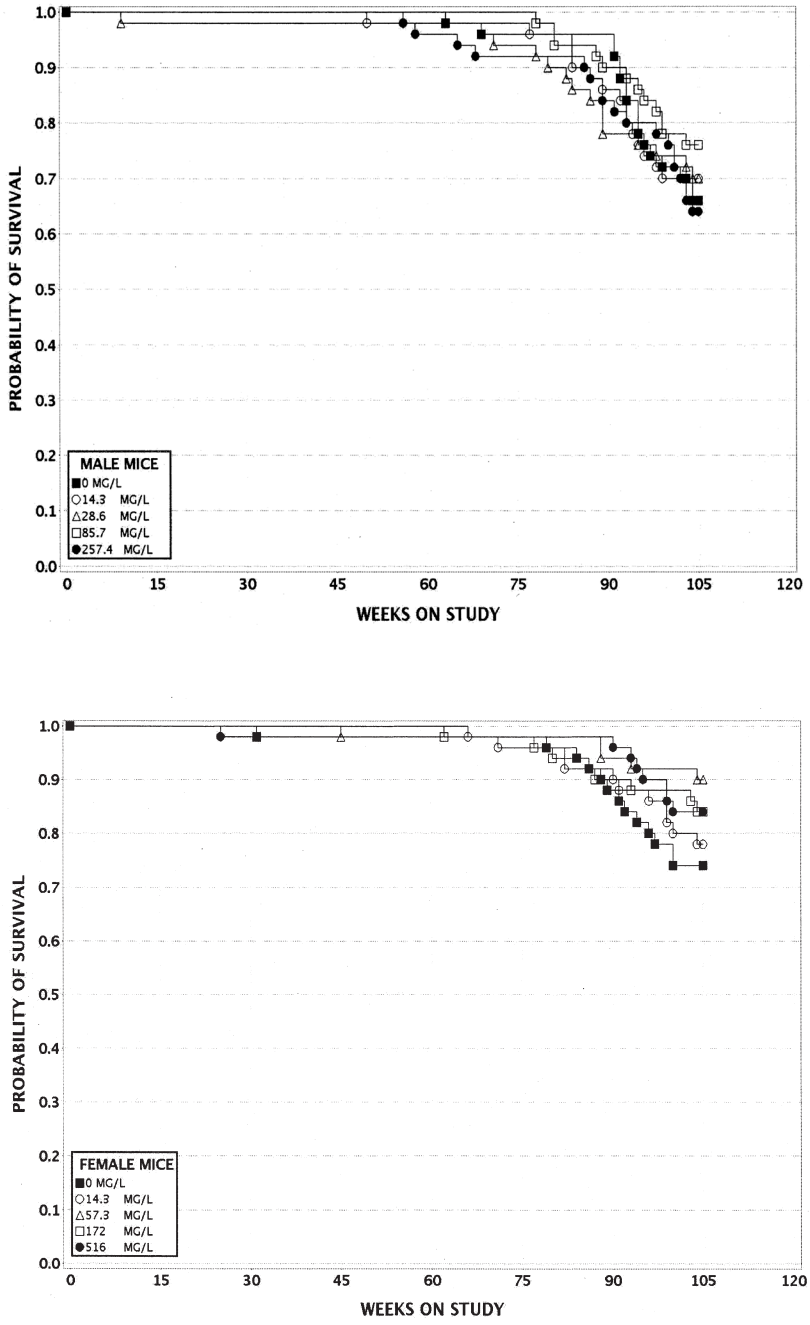


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

TABLE 10
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	0 mg/L		14.3 mg/L			28.6 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.2	50	23.2	100	50	23.5	101	50
8	25.3	50	25.3	100	50	25.7	102	50
15	26.8	50	26.9	101	50	27.1	101	50
22	28.0	50	28.2	101	50	28.5	102	50
29	29.9	50	30.0	100	50	30.3	101	50
36	31.5	50	31.5	100	50	31.9	101	50
43	32.9	50	33.0	100	50	33.4	102	50
50	34.2	50	34.5	101	50	34.8	102	50
57	35.9	50	36.3	101	50	36.6	102	50
64	37.5	50	37.8	101	50	38.2	102	49
71	38.9	50	39.4	101	50	39.9	103	49
78	40.3	50	40.6	101	50	41.2	102	49
85	41.7	50	41.8	100	50	42.4	102	49
113	46.7	50	46.5	100	50	47.2	101	49
141	48.9	50	48.7	100	50	49.2	101	49
169	50.1	50	49.9	100	50	50.2	100	49
197	51.4	50	51.8	101	50	51.8	101	49
225	52.2	50	52.6	101	50	52.5	101	49
253	52.7	50	52.7	100	50	52.7	100	49
281	53.8	50	53.8	100	50	53.7	100	49
309	53.8	50	53.6	100	50	53.9	100	49
337	54.5	50	54.6	100	50	54.7	100	49
365	55.2	50	55.0	100	49	55.0	100	49
393	55.5	50	55.2	100	49	55.2	100	49
421	55.1	50	54.9	100	49	54.1	98	49
449	55.3	49	55.0	100	49	54.4	98	49
477	55.6	49	55.2	99	49	54.2	98	49
505	55.1	48	53.7	97	49	53.6	97	47
533	54.0	48	52.6	97	48	52.9	98	47
561	54.3	48	52.5	97	48	53.1	98	45
589	53.0	48	52.1	98	45	52.3	99	43
617	52.0	48	51.6	99	44	50.7	98	42
645	51.7	44	50.7	98	41	49.3	96	39
673	51.7	38	50.5	98	37	48.8	94	38
701	50.3	36	49.9	99	35	46.9	93	37
Mean for weeks								
1-13	32.8		33.0	101		33.3	102	
14-52	51.6		51.6	100		51.8	100	
53-101	53.8		53.0	99		52.3	97	

TABLE 10
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	85.7 mg/L			257.4 mg/L		
	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.2	100	50	23.2	100	50
8	25.2	100	50	24.4	97	50
15	26.6	99	50	25.4	95	50
22	27.8	99	50	26.3	94	50
29	29.5	99	50	27.5	92	50
36	31.0	98	50	28.6	91	50
43	32.1	98	50	29.5	90	50
50	33.6	98	50	30.4	89	50
57	35.0	98	50	31.4	88	50
64	36.5	97	50	32.2	86	50
71	37.9	98	50	33.3	86	50
78	39.1	97	50	34.4	85	50
85	40.4	97	50	35.2	84	50
113	45.1	97	50	38.9	83	50
141	47.9	98	50	42.2	86	50
169	49.5	99	50	44.5	89	50
197	51.6	100	50	47.4	92	50
225	51.8	99	50	48.3	93	50
253	52.4	99	50	48.9	93	50
281	53.3	99	50	49.7	92	50
309	53.5	99	50	49.9	93	50
337	54.4	100	50	50.4	93	50
365	54.4	99	50	50.8	92	50
393	55.0	99	50	50.9	92	49
421	54.6	99	50	50.8	92	48
449	55.1	100	50	50.8	92	48
477	55.1	99	50	50.9	92	46
505	54.4	99	50	50.3	91	46
533	53.8	100	50	49.9	92	46
561	52.8	97	49	49.8	92	46
589	52.1	98	47	48.8	92	46
617	51.3	99	46	49.3	95	44
645	49.6	96	44	49.3	95	41
673	48.6	94	42	48.1	93	40
701	48.4	96	39	47.2	94	37
Mean for weeks						
1-13	32.1	98		29.4	90	
14-52	51.1	99		46.7	91	
53-101	52.7	98		49.8	93	

TABLE 11
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.8	50	17.5	99	50	17.4	98	50
9	19.2	50	19.2	100	50	19.0	99	50
16	20.6	50	20.6	100	50	20.3	98	50
23	21.3	50	21.4	100	50	21.0	99	50
30	22.5	50	22.3	99	50	21.8	97	50
37	23.2	50	23.2	100	50	22.7	98	50
44	24.4	50	24.4	100	50	23.8	98	50
51	26.0	50	25.4	98	50	24.8	96	50
58	26.9	50	26.4	98	50	25.4	95	50
65	27.9	50	27.4	98	50	26.2	94	50
72	28.9	50	28.3	98	50	27.1	94	50
79	30.3	50	29.7	98	50	28.6	94	50
86	31.2	50	31.0	99	50	29.7	95	50
114	37.0	50	36.9	100	50	34.4	93	50
142	41.5	50	41.3	100	50	38.5	93	50
170	44.8	50	44.9	100	50	41.9	93	50
198	48.7	50	48.2	99	50	46.5	96	50
226	51.6	49	51.7	100	50	48.8	95	50
254	53.3	49	53.6	101	50	50.6	95	50
282	55.2	49	55.6	101	50	52.5	95	50
310	59.0	49	57.9	98	50	55.1	93	50
338	59.8	49	59.0	99	50	56.7	95	49
366	62.1	49	62.1	100	50	60.0	97	49
394	61.5	49	60.9	99	50	59.0	96	49
422	62.2	49	62.5	100	50	60.1	97	49
450	63.1	49	62.8	100	50	61.6	98	49
478	64.3	49	64.8	101	49	62.7	97	49
506	63.9	49	65.0	102	48	62.4	98	49
534	62.7	49	64.0	102	48	61.6	98	49
562	61.8	48	62.9	102	48	60.8	99	49
590	61.3	47	62.7	102	46	59.8	98	49
618	60.3	45	62.1	103	46	59.7	99	47
646	60.6	42	61.1	101	44	58.6	97	46
674	59.8	39	60.2	101	43	58.1	97	46
702	60.6	37	60.7	100	40	58.1	96	46
Mean for weeks								
1-13	24.6		24.4	99		23.7	96	
14-52	50.1		49.9	100		47.2	94	
53-101	61.9		62.4	101		60.2	97	

TABLE 11
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Days on Study	172 mg/L Av. Wt. (g)	172 mg/L Wt. (% of controls)	172 mg/L No. of Survivors	516 mg/L Av. Wt. (g)	516 mg/L Wt. (% of controls)	516 mg/L No. of Survivors
1	17.7	100	50	17.5	99	50
9	19.1	100	50	18.4	96	50
16	20.2	98	50	19.3	93	50
23	20.8	98	50	19.9	94	50
30	21.5	96	50	20.8	93	50
37	22.4	97	50	21.3	92	50
44	23.1	95	50	22.3	92	50
51	23.9	92	50	23.3	99	50
58	24.6	92	50	23.8	89	50
65	25.2	90	50	24.6	88	50
72	25.9	89	50	24.7	86	50
79	26.8	88	50	25.5	84	50
86	27.5	88	50	26.2	84	50
114	31.4	85	50	28.6	77	50
142	35.1	85	50	30.8	74	50
170	37.6	84	50	32.8	73	49
198	41.5	85	50	36.0	74	49
226	43.7	85	50	37.5	73	49
254	45.5	85	50	38.9	73	49
282	47.8	87	50	41.0	74	49
310	50.4	85	50	43.9	74	49
338	52.7	88	50	45.4	76	49
366	55.4	89	50	48.1	78	49
394	55.8	91	50	48.4	79	49
422	57.1	92	50	49.2	79	49
450	57.7	91	49	50.0	79	49
478	59.1	92	49	51.9	81	49
506	58.4	91	49	51.9	81	49
534	57.7	92	49	51.9	83	49
562	57.6	93	47	51.8	84	49
590	57.1	93	47	51.2	84	49
618	57.5	95	45	51.6	86	49
646	56.5	93	44	50.7	84	47
674	56.1	94	44	50.8	85	45
702	55.8	92	44	51.4	85	42
Mean for weeks						
1-13	23.0	93		22.1	90	
14-52	42.9	86		37.2	74	
53-101	57.1	92		50.7	82	

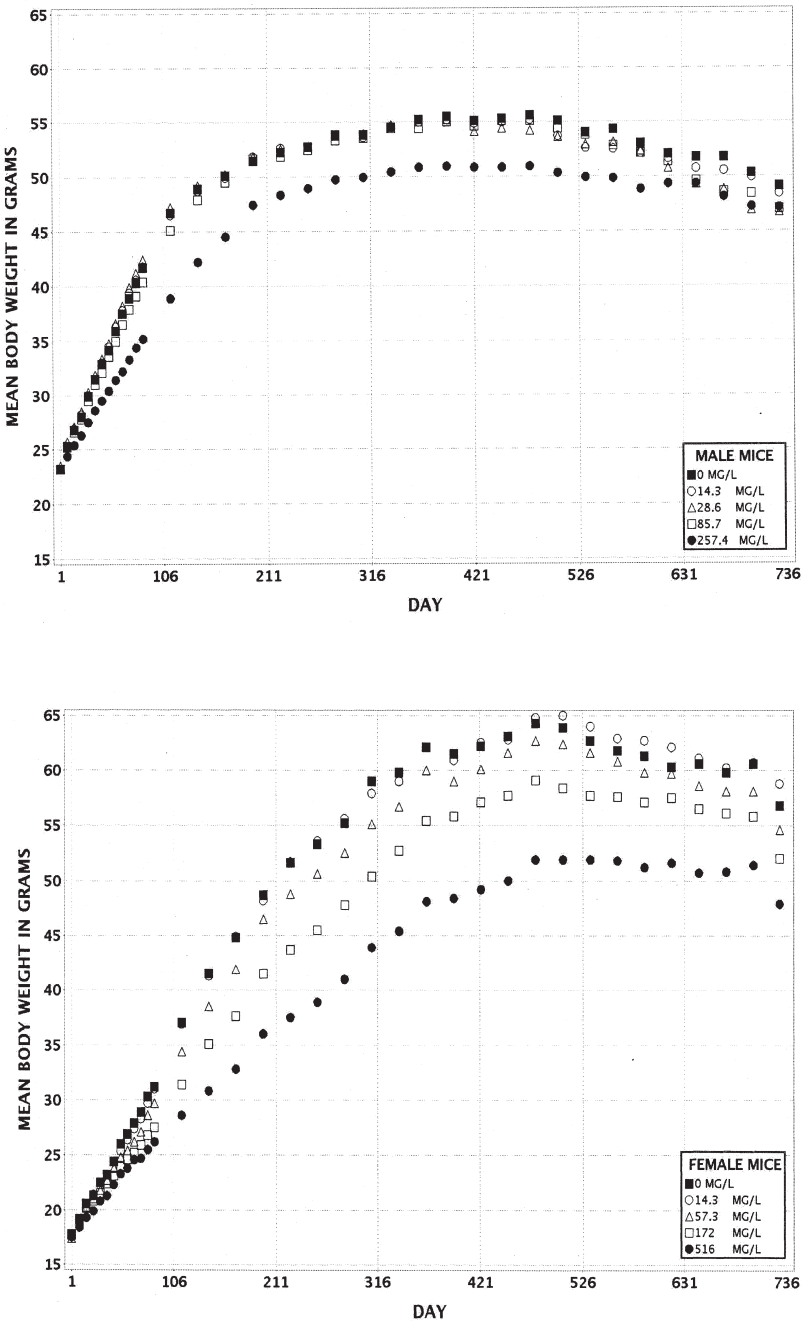


FIGURE 4
Growth Curves for Male and Female Mice Exposed to Sodium Dichromate Dihydrate in Drinking Water for 2 Years

Hematology

The hematology data for female mice in the 2-year study of sodium dichromate dihydrate are listed in Tables 12 and E2. Similar to the rat study, an exposure-related microcytosis, evidenced by decreased mean cell volume values, occurred in mice. The female mice were less affected than the male rats. A minimal (less than or equal to 8%) decrease in mean cell volume occurred at all time points; the 172 and 516 mg/L groups were consistently affected. Changes in mean cell hemoglobin values mimicked the alterations in mean cell volume and reflected the smaller erythrocytes. Erythrocyte counts demonstrated small (less than or equal to 14%) increases at all time points with the 516 mg/L group most consistently affected. However, no other estimators of the erythron demonstrated any effects.

TABLE 12
Selected Hematology Data for Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	9	10	10
Hematocrit (auto) (%)					
Day 22	50.0 ± 0.7	49.2 ± 0.4	50.0 ± 0.9	50.6 ± 0.7	49.6 ± 0.5
Month 3	47.7 ± 0.7	49.9 ± 0.5*	49.2 ± 0.8	49.4 ± 0.6	50.4 ± 0.5*
Month 6	48.4 ± 0.7	49.2 ± 0.5	47.8 ± 0.6	48.0 ± 0.8	49.2 ± 0.8
Month 12	45.0 ± 0.5	45.6 ± 0.3	45.2 ± 0.6	45.0 ± 0.7	45.1 ± 0.8
Hematocrit (spun) (%)					
Day 22	50.0 ± 0.7	49.0 ± 0.3	49.4 ± 0.8	49.6 ± 0.7	48.5 ± 0.5
Month 3	48.3 ± 0.6	50.4 ± 0.5*	49.3 ± 0.6	49.4 ± 0.5	50.4 ± 0.4*
Month 6	49.0 ± 0.6	50.2 ± 0.5	48.7 ± 0.5	48.9 ± 0.8	49.9 ± 0.7
Month 12	46.5 ± 0.4	47.4 ± 0.2	46.9 ± 0.5	46.4 ± 0.6	46.7 ± 0.6
Hemoglobin (g/dL)					
Day 22	16.8 ± 0.2	16.5 ± 0.1	16.7 ± 0.3	16.9 ± 0.2	16.4 ± 0.2
Month 3	16.0 ± 0.2	16.7 ± 0.2*	16.4 ± 0.3	16.3 ± 0.2	16.5 ± 0.2
Month 6	16.1 ± 0.2	16.4 ± 0.2	16.0 ± 0.2	16.0 ± 0.3	16.2 ± 0.3
Month 12	14.9 ± 0.1	15.3 ± 0.2	15.1 ± 0.2	15.0 ± 0.2	14.9 ± 0.3
Erythrocytes (10^6/µL)					
Day 22	10.25 ± 0.15	10.20 ± 0.08	10.47 ± 0.19	10.77 ± 0.13*	10.61 ± 0.13*
Month 3	10.10 ± 0.16	10.66 ± 0.13*	10.55 ± 0.17*	10.95 ± 0.10**	11.55 ± 0.16**
Month 6	10.56 ± 0.15	10.81 ± 0.10	10.60 ± 0.13	10.77 ± 0.20	11.50 ± 0.20**
Month 12	9.58 ± 0.10	9.72 ± 0.09	9.77 ± 0.10	9.95 ± 0.13*	10.30 ± 0.21**
Reticulocytes (10^6/µL)					
Day 22	0.32 ± 0.01	0.30 ± 0.01	0.33 ± 0.02	0.31 ± 0.01	0.32 ± 0.02
Month 3	0.33 ± 0.01	0.31 ± 0.01	0.34 ± 0.02	0.34 ± 0.03	0.34 ± 0.02
Month 6	0.36 ± 0.02	0.37 ± 0.01	0.39 ± 0.04	0.36 ± 0.03	0.35 ± 0.02
Month 12	0.32 ± 0.02	0.33 ± 0.01	0.32 ± 0.01	0.36 ± 0.02	0.37 ± 0.02
Nucleated erythrocytes (10^3/µL)					
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 6	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 12	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)					
Day 22	48.8 ± 0.2	48.3 ± 0.1*	47.8 ± 0.2**	47.0 ± 0.2**	46.8 ± 0.2**
Month 3	47.2 ± 0.1	46.9 ± 0.3	46.7 ± 0.1	45.1 ± 0.2**	43.7 ± 0.3**
Month 6	45.8 ± 0.2	45.5 ± 0.3	45.1 ± 0.2*	44.6 ± 0.2**	42.8 ± 0.3**
Month 12	46.9 ± 0.3	46.9 ± 0.3	46.3 ± 0.3	45.2 ± 0.2**	43.9 ± 0.5**
Mean cell hemoglobin (pg)					
Day 22	16.4 ± 0.1	16.2 ± 0.0*	15.9 ± 0.1**	15.7 ± 0.1**	15.5 ± 0.1**
Month 3	15.8 ± 0.0	15.7 ± 0.1	15.6 ± 0.0**	14.9 ± 0.1**	14.3 ± 0.1**
Month 6	15.3 ± 0.1	15.2 ± 0.1	15.1 ± 0.1	14.9 ± 0.1**	14.1 ± 0.1**
Month 12	15.5 ± 0.1	15.7 ± 0.2	15.5 ± 0.1	15.1 ± 0.1*	14.4 ± 0.2**
Mean cell hemoglobin concentration (g/dL)					
Day 22	33.6 ± 0.1	33.5 ± 0.1	33.3 ± 0.2	33.4 ± 0.1	33.1 ± 0.1**
Month 3	33.5 ± 0.1	33.5 ± 0.1	33.3 ± 0.1	33.1 ± 0.1**	32.8 ± 0.1**
Month 6	33.4 ± 0.2	33.4 ± 0.1	33.5 ± 0.2	33.4 ± 0.1	32.9 ± 0.1
Month 12	33.1 ± 0.2	33.5 ± 0.2	33.4 ± 0.1	33.3 ± 0.1	32.9 ± 0.1

* 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. Statistical tests were performed on unrounded data.
[b] n=9

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the small intestine (duodenum, jejunum, ileum), liver, mesenteric lymph node, pancreatic lymph node, and pancreas. Summaries of the incidences of neoplasms and nonneoplastic lesions, 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 Appendix C for male mice and Appendix D for female mice.

Small Intestine (Duodenum, Jejunum, and Ileum): In the duodenum, the incidences of adenoma occurred with a positive trend in males and females. The incidences of adenoma in 257.4 mg/L males and 172 and 516 mg/L females were significantly greater that those in the controls (Tables 13, C2, and D2). The incidences of multiple adenoma were also significantly increased in 257.4 mg/L males and in 516 mg/L females. Adenomas were observed in one control, one 28.6 mg/L, and five 85.7 mg/L males and in two 57.3 mg/L females; none of these increased incidences were statistically significant. However, the incidences of adenoma in 85.7 mg/L males and 57.3 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13, C3, and D3). The incidences of carcinoma of the duodenum were increased in 85.7 and 257.4 mg/L males and in 172 and 516 mg/L females; the incidence in 516 mg/L females was significantly greater than that in the controls. The incidences of carcinoma in 257.4 mg/L males and 516 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration.

In the jejunum, the incidence of adenoma in 516 mg/L females was significantly increased compared to that in the controls (Tables 13 and D2). In females, one adenoma occurred in the 14.3 mg/L group and two adenomas occurred in the 172 mg/L group; the incidence in 172 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13, C3, and D3). The incidence of adenoma was greater in 257.4 mg/L males but was not significantly increased compared to the controls. However, the incidence exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13 and C3). In the historical controls for the jejunum, adenoma has not been observed in mice in drinking water studies, and only one adenoma has been observed in males for all routes of administration. Low incidences of carcinoma of the jejunum occurred in exposed male and female mice; in males, the incidences of carcinoma in the 14.3, 85.7, and 257.4 mg/L groups did not exceed the historical control ranges for drinking water studies or for all routes of administration (Tables 13, C2, and C3). In females, the incidences of carcinoma of the jejunum in the 57.3 and 172 mg/L groups exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13, D2, and D3).

For the entire small intestine (duodenum, jejunum, and ileum), the incidences of adenoma and carcinoma in 257.4 mg/L males and the incidences of adenoma or carcinoma (combined) in 85.7 and 257.4 mg/L males were significantly greater than those in the controls. The incidences of adenoma in 85.7 mg/L males exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13, C2, and C3). For the entire small intestine, the incidence of adenoma in 172 mg/L females, the incidences of adenoma and carcinoma in 516 mg/L females, and the incidences of adenoma or carcinoma (combined) in 172 and 516 mg/L females were significantly increased. The incidences of adenoma, carcinoma, and adenoma or carcinoma (combined) in 57.3 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13, D2, and D3). The incidences of carcinoma in 172 mg/L females exceeded the historical control ranges for drinking water studies and for all routes of administration (Tables 13 and D3).

Adenomas were discrete, broad based, focally extensive, plaque-like lesions that thickened the mucosa and protruded into the lumen (Plates 13 and 14). They were composed of irregular, elongated, often branching crypts and irregular, glandular structures lined by one to several layers of densely packed, atypical, cuboidal to tall columnar, hyperchromatic epithelial cells with large oval to elongated nuclei. Increased mitotic activity was commonly evident.

Carcinomas were extensive, sessile, plaque-like neoplasms distinguished from adenomas by dysplastic epithelial growth, complete effacement of the mucosa with invasion of the submucosa and/or muscularis mucosa, degree of cellular atypia, and the presence of variable fibroplasia/desmoplasia (Plates 15 and 16). They were composed of hyperchromatic, atypical, pleomorphic

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions in the Small Intestine of Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Number Necropsied	50	50	50	50	50
Duodenum					
Epithelium, Hyperplasia, Focal[a]	0	0	0	1 (3.0)[b]	2 (3.5)
Epithelium, Hyperplasia, Diffuse	0	11** (2.0)	18** (1.6)	42** (2.1)	32** (2.1)
Infiltration Cellular, Histiocyte	0	2 (1.0)	4 (1.0)	37** (1.2)	35** (1.7)
Adenoma, Multiple	0	0	0	0	6*
Adenoma (includes multiple)[c]					
Overall Rate[d]	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)	15/50 (30%)
Adjusted Rate[e]	2.2%	0.0%	2.3%	10.8%	32.9%
Terminal Rate[f]	0/33 (0%)	0/35 (0%)	1/35 (3%)	5/38 (13%)	10/32 (31%)
First Incidence (days)	665	—[h]	729 (T)	729 (T)	451
Poly-3 Test[g]	P<0.001	P=0.505N	P=0.751	P=0.106	P<0.001
Carcinoma[i]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rate	0.0%	0.0%	0.0%	4.3%	6.8%
Terminal Rate	0/33 (0%)	0/35 (0%)	0/35 (0%)	2/38 (5%)	3/32 (9%)
First Incidence (days)	—	—[j]	—	729 (T)	729 (T)
Poly-3 Test	P=0.011		—	P=0.243	P=0.113
Jejunum					
Adenoma[k]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rate	0.0%	0.0%	0.0%	0.0%	6.8%
Terminal Rate	0/33 (0%)	0/35 (0%)	0/35 (0%)	0/38 (0%)	2/32 (6%)
First Incidence (days)	—	—	—	—	714
Poly-3 Test	P=0.002	—	—	—	P=0.114
Carcinoma, Multiple	0	1	0	0	0
Carcinoma (includes multiple)[l]	0	2	0	1	2
Duodenum, Jejunum, or Ileum					
Adenoma[m]					
Overall Rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)	17/50 (34%)
Adjusted Rate	2.2%	2.3%	2.3%	10.8%	37.2%
Terminal Rate	0/33 (0%)	1/35 (3%)	1/35 (3%)	5/38 (13%)	11/32 (34%)
First Incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 Test	P<0.001	P=0.755	P=0.751	P=0.106	P<0.001
Carcinoma[n]					
Overall Rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rate	0.0%	4.5%	2.3%	6.5%	11.4%
Terminal Rate	0/33 (0%)	2/35 (6%)	1/35 (3%)	3/38 (8%)	5/32 (16%)
First Incidence (days)	—	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 Test	P=0.014	P=0.233	P=0.492	P=0.123	P=0.028
Adenoma or Carcinoma[o]					
Overall Rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	7/50 (14%)	20/50 (40%)
Adjusted Rate	2.2%	6.8%	4.6%	15.1%	43.8%
Terminal Rate	0/33 (0%)	3/35 (9%)	2/35 (6%)	7/38 (18%)	14/32 (44%)
First Incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 Test	P<0.001	P=0.296	P=0.485	P=0.032	P<0.001

TABLE 13
Incidences of Neoplastic and Nonneoplastic Lesions in the Small Intestine of Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female					
Number Necropsied	50	50	50	50	50
Duodenum					
Epithelium, Hyperplasia, Focal	0	0	1 (2.0)	2 (3.0)	0
Epithelium, Hyperplasia, Diffuse	0	16** (1.6)	35** (1.7)	31** (1.6)	42** (2.2)
Infiltration Cellular, Histiocyte	0	0	4 (1.3)	33** (1.2)	40** (2.0)
Adenoma, Multiple	0	0	0	1	6*
Adenoma (includes multiple)[p]					
Overall Rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	13/50 (26%)	12/50 (24%)
Adjusted Rate	0.0%	0.0%	4.2%	27.8%	25.2%
Terminal Rate	0/37 (0%)	0/39 (0%)	2/45 (4%)	13/42 (31%)	11/42 (26%)
First Incidence (days)	—	—	729 (T)	729 (T)	693
Poly-3 Test	P<0.001	—	P=0.251	P<0.001	P<0.001
Carcinoma[q]					
Overall Rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rate	0.0%	0.0%	0.0%	2.1%	12.6%
Terminal Rate	0/37 (0%)	0/39 (0%)	0/45 (0%)	1/42 (2%)	5/42 (12%)
First Incidence (days)	—	—	—	729 (T)	625
Poly-3 Test	P<0.001	—	—	P=0.507	P=0.019
Jejunum					
Epithelium, Hyperplasia, Diffuse	0	2 (2.0)	1 (2.0)	0	8** (1.9)
Infiltration Cellular, Histiocyte	0	0	0	2 (1.0)	8** (1.6)
Adenoma, Multiple	0	0	0	0	1
Adenoma (includes multiple)[r]					
Overall Rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rate	0.0%	2.2%	0.0%	4.3%	10.6%
Terminal Rate	0/37 (0%)	1/39 (3%)	0/45 (0%)	2/42 (5%)	5/42 (12%)
First Incidence (days)	—	729 (T)	—	729 (T)	729 (T)
Poly-3 Test	P=0.002	P=0.504	—	P=0.246	P=0.035
Carcinoma[s]	1	0	2	2	1
Duodenum, Jejunum, or Ileum					
Adenoma[t]					
Overall Rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	15/50 (30%)	16/50 (32%)
Adjusted Rate	0.0%	2.2%	4.2%	32.0%	33.7%
Terminal Rate	0/37 (0%)	1/39 (3%)	2/45 (4%)	15/42 (36%)	15/42 (36%)
First Incidence (days)	—	729 (T)	729 (T)	729 (T)	693
Poly-3 Test	P<0.001	P=0.504	P=0.251	P<0.001	P<0.001
Carcinoma[u]					
Overall Rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted Rate	2.2%	0.0%	4.2%	6.4%	14.7%
Terminal Rate	1/37 (3%)	0/39 (0%)	2/45 (4%)	3/42 (7%)	6/42 (14%)
First Incidence (days)	729 (T)	—	729 (T)	729 (T)	625
Poly-3 Test	P<0.001	P=0.496N	P=0.521	P=0.319	P=0.037

TABLE 13
Incidences of Neoplastic and Nonneoplastic Lesions in the Small Intestine of Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Female (continued)					
Adenoma or Carcinoma[v]					
Overall Rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	17/50 (34%)	22/50 (44%)
Adjusted Rate	2.2%	2.2%	8.3%	36.3%	45.9%
Terminal Rate	1/37 (3%)	1/39 (3%)	4/45 (9%)	17/42 (41%)	20/42 (48%)
First Incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)	625
Poly-3 Test	P<0.001	P=0.756N	P=0.198	P<0.001	P<0.001

(T) Terminal sacrifice
* Significantly different (P≤0.05) from the control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year drinking water studies with controls given NTP-2000 diet (mean ± standard deviation): 6/299 (2.0% ± 2.2%), range 0%-6%; all routes: 9/1,549 (0.6% ± 1.3%), range 0%-6%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence for drinking water studies: 1/299 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,549 (0.2% ± 0.8%), range 0%-4%
[j] Value of statistic cannot be computed.
[k] Historical incidence for drinking water studies: 0/299; all routes: 1/1,549 (0.1% ± 0.4%), range 0%-2%
[l] Historical incidence for drinking water studies: 5/299 (1.7% ± 1.5%), range 0%-4%; all routes: 25/1,549 (1.6% ± 2.2%), range 0%-8%
[m] Historical incidence for drinking water studies: 6/299 (2.0% ± 2.2%), range 0%-6%; all routes: 10/1,549 (0.7% ± 1.3%), range 0%-6%
[n] Historical incidence for drinking water studies: 6/299 (2.0% ± 1.8%), range 0%-4%; all routes: 30/1,549 (2.0% ± 2.2%), range 0%-8%
[o] Historical incidence for drinking water studies: 11/299 (3.7% ± 3.7%), range 0%-10%; all routes: 39/1,549 (2.6% ± 2.7%), range 0%-10%
[p] Historical incidence for drinking water studies: 1/350 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,648 (0.2% ± 0.6%), range 0%-2%
[q] Historical incidence for drinking water studies: 0/350; all routes: 1/1,648 (0.1% ± 0.4%), range 0%-2%
[r] Historical incidence for drinking water studies: 0/350; all routes: 0/1,648
[s] Historical incidence for drinking water studies: 2/350 (0.6% ± 1.0%), range 0%-2%; all routes: 5/1,648 (0.3% ± 0.7%), range 0%-2%
[t] Historical incidence for drinking water studies: 1/350 (0.3% ± 0.8%), range 0%-2%; all routes: 3/1,648 (0.2% ± 0.6%), range 0%-2%
[u] Historical incidence for drinking water studies: 3/350 (0.9% ± 1.1%), range 0%-2%; all routes: 8/1,648 (0.5% ± 0.8%), range 0%-2%
[v] Historical incidence for drinking water studies: 4/350 (1.1% ± 1.6%), range 0%-4%; all routes: 11/1,648 (0.7% ± 1.1%), range 0%-4%

(cuboidal, round, polygonal, columnar) epithelial cells that had round, oval, or elongated hyperchromatic nuclei. Increased mitotic activity was evident to a greater extent than in adenomas, and many mitoses were atypical.

Low incidences of focal epithelial hyperplasia occurred in the duodenum of exposed male and female mice (Tables 13, C4, and D4). Although the increased incidences were not exposure concentration-related or statistically significant, this lesion was considered a preneoplastic lesion related to exposure to sodium dichromate dihydrate because of its morphologic similarities to adenoma. Focal epithelial hyperplasias were distinguished from adenomas in that they were smaller, commonly located in the superficial mucosa, and were less discrete with margins that tended to blend with the normal surrounding mucosal epithelium. These hyperplastic lesions occurred as focal disorganized areas of increased cellularity that stained more basophilic than the surrounding histologically normal mucosa (Plates 17 and 18). They were composed of crypts and villi that were lined by increased numbers of cuboidal to tall columnar epithelial cells that were morphologically similar to those of the adenomas.

The incidences of diffuse epithelial hyperplasia were significantly increased in the duodenum of all exposed groups of male and female mice (Tables 13, C4, and D4). In the jejunum, the incidence of diffuse epithelial hyperplasia was significantly increased in 516 mg/L females. Diffuse epithelial hyperplasia generally involved the entire mucosa. Compared to the controls, the duodenal villi of exposed mice were short, broad, blunt, and lined by densely packed, tall columnar epithelial cells that were more basophilic than the shorter epithelial cells lining the duodenum villi of the controls (Plates 19 to 22). The epithelial cells and cell nuclei were often piled up in multiple layers along the long axis of the villi. Intestinal crypts were often elongated and generally appeared to contain increased numbers of epithelial cells with increased numbers of mitotic figures. Collectively, these lesions are considered consistent with regenerative hyperplasia secondary to previous epithelial cell injury.

The incidences of histiocytic cellular infiltration were significantly increased in the duodenum of 85.7 and 257.4 mg/L males and of 172 and 516 mg/L females (Tables 13, C4, and D4). In the jejunum, the incidence of histiocytic cellular infiltration was significantly increased in 516 mg/L females compared to the controls. Histiocyte infiltrates in the duodenum and jejunum were consistent with those observed in the duodenum of rats. Infiltrates ranged from small clusters of three to five cells in the lower exposure groups to larger clusters that expanded the tips of the affected villi in the higher exposure groups.

Liver: The incidences of hepatoblastoma in 14.3, 85.7, and 257.4 mg/L males were significantly less than that in the controls (0 mg/L, 17/50; 14.3 mg/L, 8/50; 28.6 mg/L, 11/50; 85.7 mg/L, 2/50; 257.4 mg/L, 0/50; Table C2). The incidences of hepatocellular adenoma or carcinoma (combined) in 28.6 mg/L males (42/50, 42/50, 33/50, 37/50, 41/50) and hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) in 28.6 and 85.7 mg/L males (46/50, 42/50, 37/50, 37/50, 41/50) were significantly decreased. The incidences of hepatocellular adenoma in 172 and 516 mg/L females were significantly less than that in the controls (0 mg/L, 14/49; 14.3 mg/L, 21/50; 57.3 mg/L, 13/50; 172 mg/L, 6/50; 516 mg/L, 3/50; Table D2). The biological significance of these decreases is unknown.

The incidences of histiocytic cellular infiltration were significantly increased in all exposed groups of females (Tables 14 and D4). The incidence of chronic inflammation was significantly increased in 172 mg/L females. The incidences of histiocytic cellular infiltration and chronic inflammation in female mice were consistent with those observed in rats. The incidence of clear cell focus in 257.4 mg/L males was significantly less than that in the controls (Tables 14 and C4). The incidences of eosinophilic focus in 257.4 mg/L males and 172 and 516 mg/L females were significantly less than those in the controls.

Mesenteric Lymph Node: The incidences of minimal to moderate histiocytic cellular infiltration in all exposed groups of male and female mice were significantly greater than those in the controls (Tables 14, C4, and D4). In general, there was a slight increase in the severity with increasing exposure concentration. Histiocytic cellular infiltration in mice was consistent with that observed in rats.

Pancreatic Lymph Node: The incidences of minimal to moderate histiocytic cellular infiltration in 85.7 and 257.4 mg/L males and in 172 and 516 mg/L females were significantly greater than those in the controls (Tables 14, C4, and D4). Histiocytic cellular infiltration in mice was consistent with that observed in rats.

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Male					
Liver[a]	50	50	50	50	50
Clear Cell Focus[b]	20	17	19	16	7**
Eosinophilic Focus	27	26	19	21	12**
Lymph Node, Mesenteric	47	47	49	49	46
Infiltration Cellular, Histiocyte	14 (1.2)[c]	38** (1.1)	31** (1.2)	32** (1.5)	42** (2.5)
Lymph Node, Pancreatic	5	13	10	8	16
Infiltration Cellular, Histiocyte	0	2 (1.0)	2 (1.0)	5* (1.4)	12** (2.3)
Pancreas	49	49	50	49	48
Acinus, Cytoplasmic Alteration	0	1 (3.0)	1 (3.0)	9** (2.1)	8** (2.6)
	0 mg/L	**14.3 mg/L**	**57.3 mg/L**	**172 mg/L**	**516 mg/L**
Female					
Liver	49	50	50	50	50
Infiltration Cellular, Histiocyte	2 (1.0)	15** (1.1)	23** (1.0)	32** (1.0)	45** (1.9)
Inflammation, Chronic	16 (1.1)	21 (1.1)	22 (1.1)	27* (1.1)	24 (1.0)
Eosinophilic Focus	14	18	8	5*	4**
Lymph Node, Mesenteric	46	48	46	50	50
Infiltration Cellular, Histiocyte	3 (1.0)	29** (1.3)	26** (1.1)	40** (1.9)	42** (2.7)
Lymph Node, Pancreatic	14	12	15	14	13
Infiltration Cellular, Histiocyte	0	1 (1.0)	2 (1.5)	7** (1.9)	8** (2.5)
Pancreas	48	50	49	50	50
Acinus, Cytoplasmic Alteration	0	6* (2.5)	6* (2.0)	14** (2.4)	32** (2.6)

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

Pancreas: The incidences of cytoplasmic alteration in the pancreatic acini of males exposed to 85.7 or 257.4 mg/L and in all exposed groups of females were significantly increased (Tables 14, C4, and D4). Cytoplasmic alteration was characterized by depletion of cytoplasmic zymogen granules from the pancreatic acinar epithelial cells. The biological significance of this change was uncertain.

CHROMIUM TISSUE DISTRIBUTION STUDY

As part of the 2-year study, total chromium concentration in selected tissues and excreta were determined in additional groups of animals (tissue distribution groups) composed of male rats and female mice (Appendix J). These animals were treated the same as the animals in the core study groups with respect to exposure, housing, and handling. Two days prior to scheduled tissue collection, up to 10 animals in each exposure group of both species were placed in individual metabolism cages for the separate collection of urine and feces. Animals were provided undosed drinking water during this time to allow unabsorbed chromium to be excreted. The 48-hour washout period was based on an elimination half-life of 8 to 21 hours (Bragt and van Dura, 1983; Vanoirbeek *et al.*, 2003). Increased chromium concentrations in plasma after the washout period should represent the chromium entering plasma from the tissues. Insufficient mouse urine was collected for analysis at most time points; incomplete separation of urine and feces and low urine volumes for mice are typical in metabolism cages. After 48 hours, the animals were euthanized, and erythrocytes, plasma, liver, kidney, glandular stomach, and forestomach were removed for chromium analysis. The analytical procedure could not differentiate between the oxidation states of chromium, so the values reported are for total chromium irrespective of oxidation state. The complete data sets for rats and mice are presented in Tables J1 and J2, respectively.

Chromium concentration in tissues from the 172 and 516 mg/L rats and mice were significantly higher than their respective controls on days 6, 13, 182, and 371, with the exception of the forestomach on day 6. In the 57.3 mg/L rats, chromium concentrations in the glandular stomach were also significantly elevated at all four time points, while concentrations in the liver and kidney were elevated at three of the four time points. In the 57.3 mg/L mice, chromium concentrations in the liver, kidney, and glandular stomach were significantly elevated at all four time points. In the 14.3 mg/L rats, chromium concentrations were significantly elevated above the controls in the glandular stomach on days 6, 13, and 182, in the kidney on days 13, 182, and 371, and in the liver on days 182 and 371. In the 14.3 mg/L mice, chromium concentrations were significantly elevated in the liver and kidney at all four time points. In the lowest exposed group, chromium concentrations in erythrocytes and the forestomach were generally similar to those in control rats and mice. In all tissues, the chromium concentration at each time point tended to increase as the exposure concentration increased; however, the increases were not proportional to exposure concentration as shown for the liver in Figure 5. A nonproportional increase in tissue concentration with increasing exposure concentration is consistent with saturation of an active uptake mechanism for Cr VI. In accumulating tissues, such as the kidney, liver, forestomach, and glandular stomach, chromium concentration increased through day 371, but the increases were not proportional to the duration of exposure (Figure 6). In nonaccumulating tissues such as erythrocytes, chromium concentration did not increase after day 6. This observation can be interpreted as the tissues approaching equilibrium between Cr VI uptake and Cr III diffusion from the tissues and from cell turnover. In addition, there was a slight decrease in chromium exposure per day as the animals aged, based on decreased water consumption and increased body weight (Tables 3, 11, G1, and G4), which was also reflected in lower chromium concentration in feces at the later time points. In rats and mice, the tissues with the highest chromium concentrations were the glandular stomach, kidney, and liver. Mean concentrations of chromium in the kidney were greater than those in the liver at most time points for rats, whereas, the reverse was generally true for mice. Most of the ingested chromium was excreted in the feces of both species. The 48-hour feces collection contained up to 2 mg of chromium for rats and 160 µg for mice. The 48-hour urine collection from rats contained up to 20 µg total chromium, but urine collection from mice was unsuccessful as noted above.

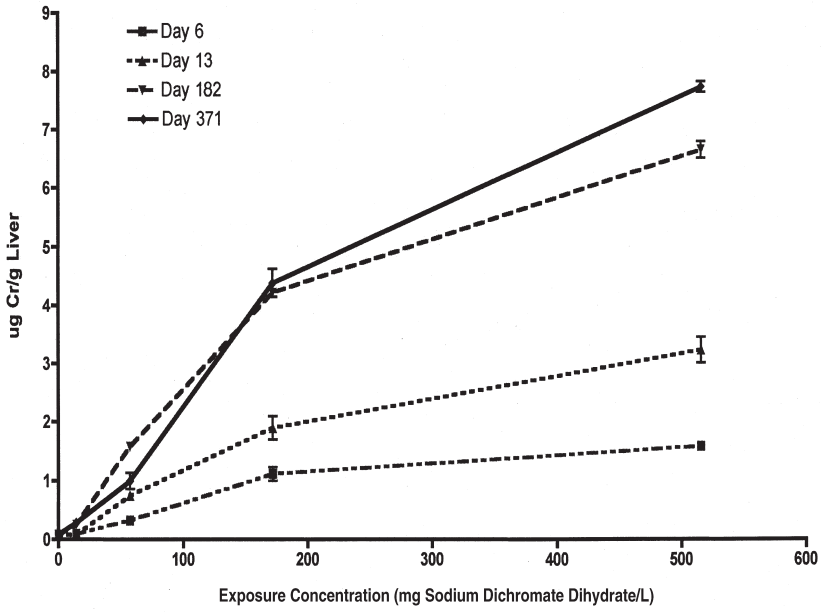


FIGURE 5
Chromium Concentrations on Days 6, 13, 182, and 371 in the Liver of Male Rats Exposed to Sodium Dichromate Dihydrate in Drinking Water

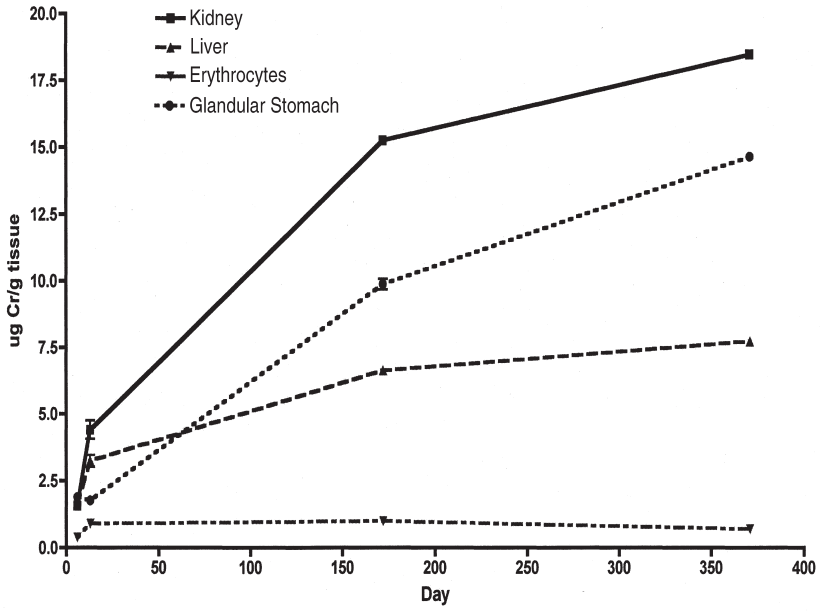


FIGURE 6
Chromium Concentrations in the Kidney, Liver, Erythrocytes, and Glandular Stomach of Male Rats Exposed to 516 mg/L Sodium Dichromate Dihydrate in Drinking Water

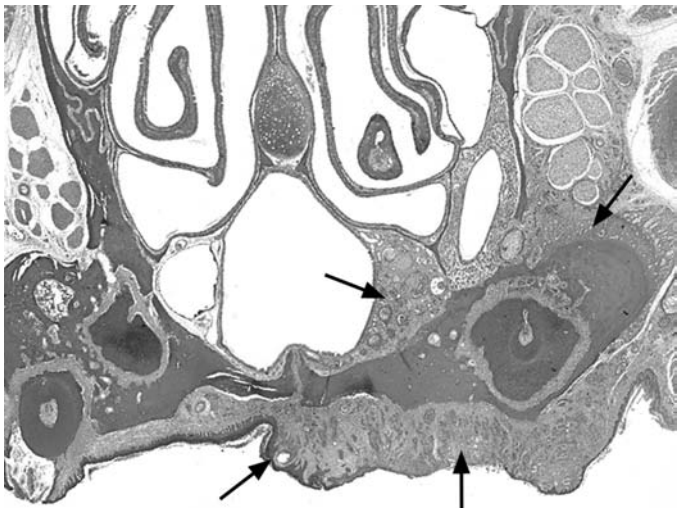


PLATE 1
Low magnification of a section of the nasal cavity demonstrating the location of a squamous cell carcinoma (arrows) arising from the oral mucosa of the soft palate that has invaded the adjacent submucosal tissue and surrounded a molar tooth. Male rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

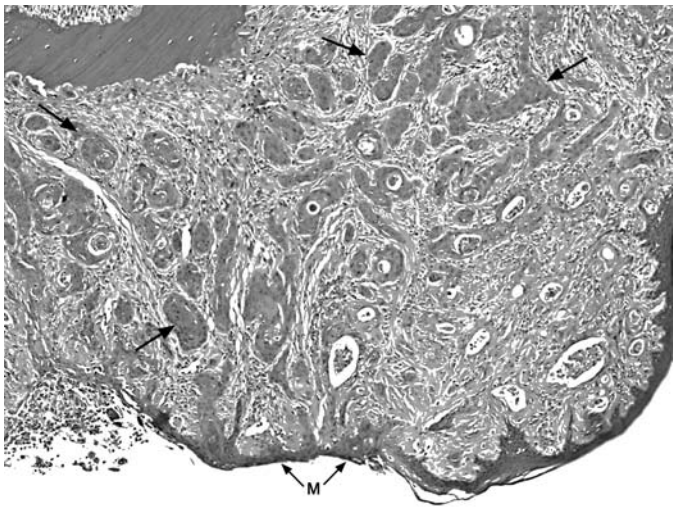


PLATE 2
Higher magnification of Plate 1 demonstrating the malignant features of the squamous cell carcinoma. The neoplasm is composed of pleomorphic islands, cords, and clusters of dysplastic squamous epithelium (arrows) surrounded by dense proliferative connective tissue stroma. Oral mucosa (M). H&E

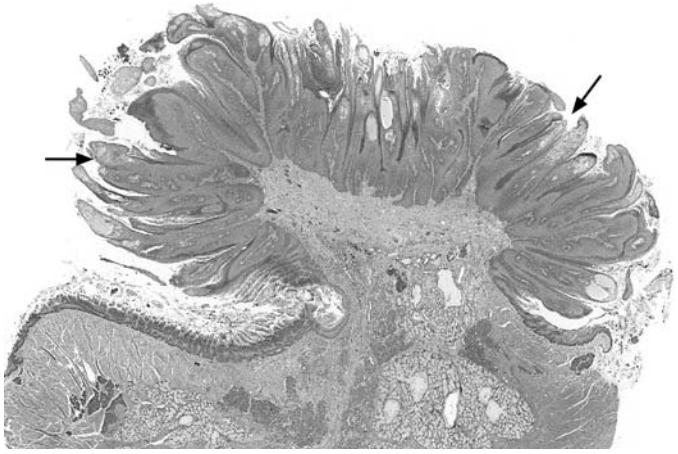


PLATE 3
Squamous cell carcinoma projecting from the dorsal mucosal surface of the tongue (arrows). The carcinoma is composed of thick papillae of well-differentiated, mature, keratinized squamous epithelium (arrows) supported by connective tissue stroma. Female rat exposed to 14.3 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

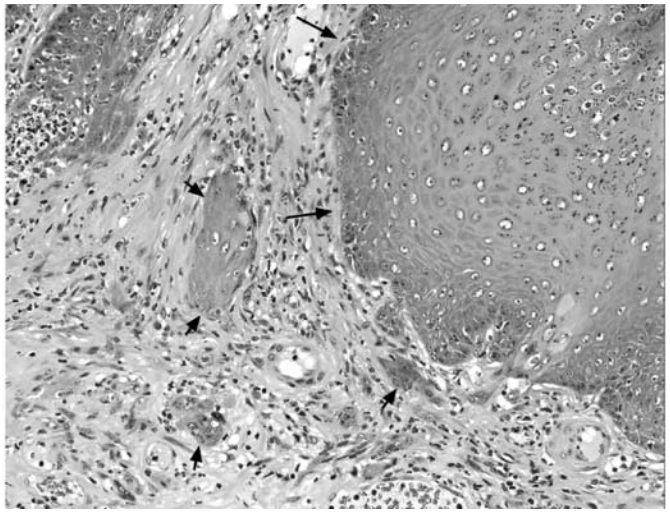


PLATE 4
Higher magnification of Plate 3. Note foci of dysplastic epithelium (short arrows) within the stroma and extending from the base of the surface epithelium (arrows). H&E

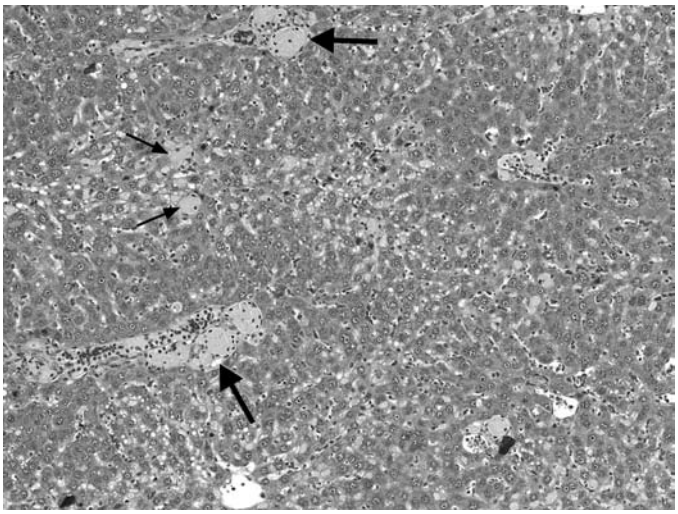


PLATE 5
Liver demonstrating histiocytic cellular infiltrates within the parenchyma (thin arrows) and in portal areas (thick arrows). Female rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

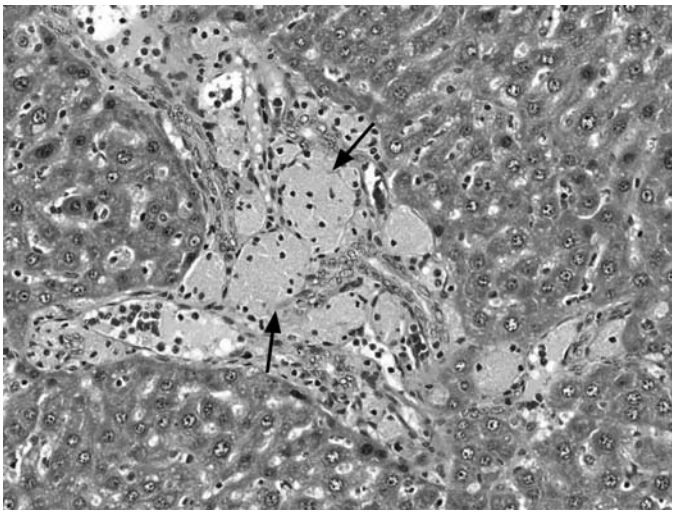


PLATE 6
Higher magnification of the histiocytic cellular infiltrates (arrows) within a portal area. Histiocytes have abundant pale, lightly eosinophilic, faintly stippled cytoplasm and single, small, dark peripheral nuclei. Female rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

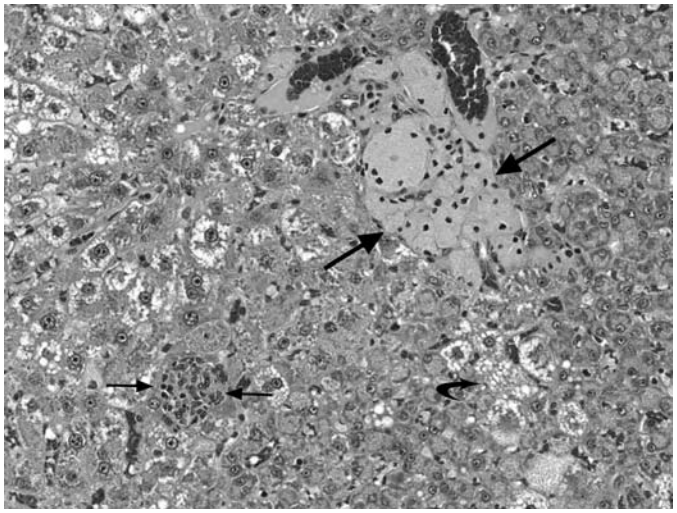


PLATE 7
Liver demonstrating focal chronic inflammation (thin arrows) composed of a mixture of lymphocytes and small macrophages. Note also adjacent histiocytic infiltrates within a portal area (thick arrows) and hepatocytes with fatty change (curved arrow). Female rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

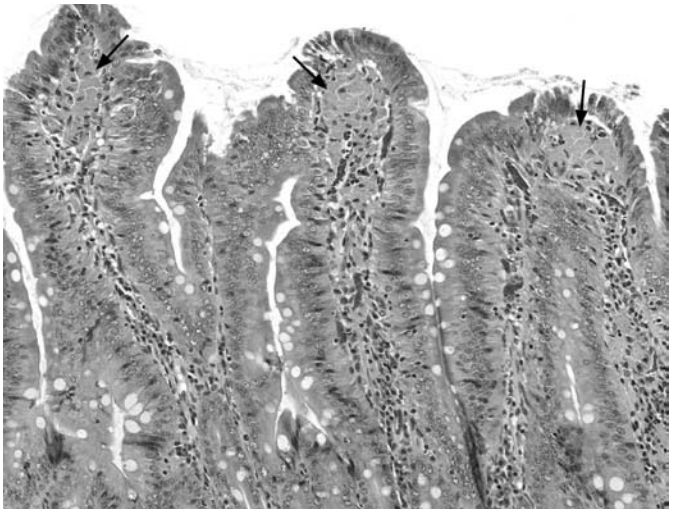


PLATE 8
Duodenum demonstrating histiocytic cellular infiltrates (arrows) within the lamina propria at the tips of the villi. Male rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

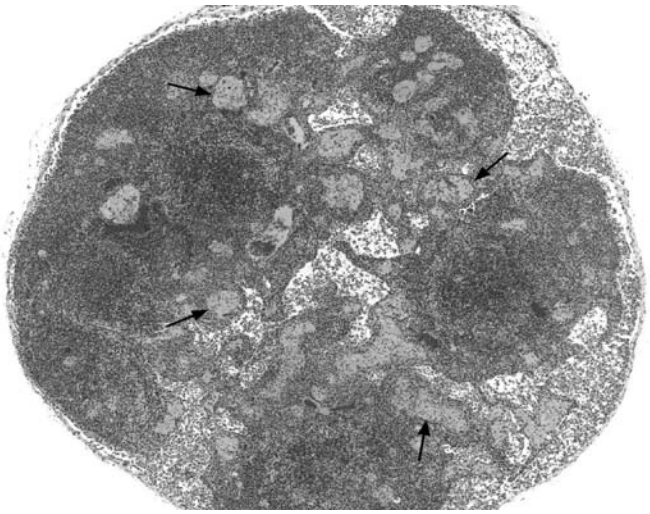


PLATE 9
Low magnification of a mesenteric lymph node demonstrating variably sized clusters and syncytia of histiocytic cellular infiltrates (arrows) within the parenchyma and sinusoids. Female rat exposed to 172 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

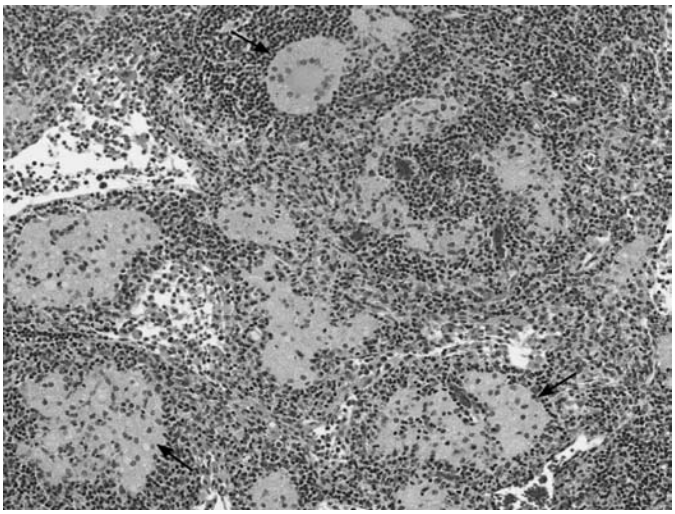


PLATE 10
agnification of Plate 9. Note that the histiocytes have coalesced to form irregularly sized syncytia (arrows). H&E

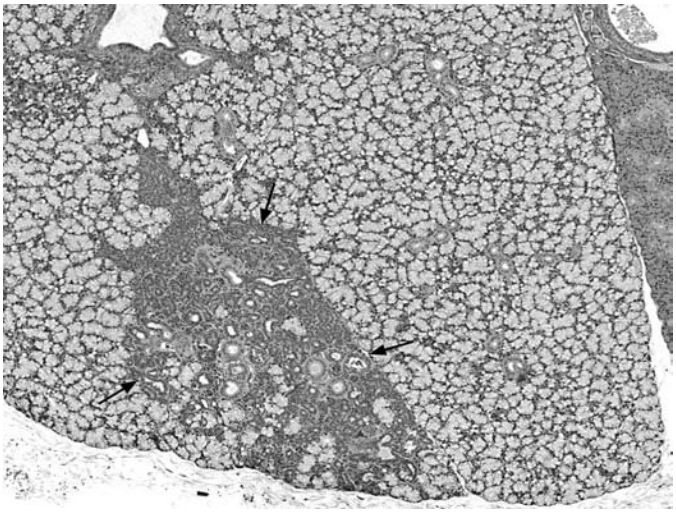


PLATE 11
Low magnification demonstrating a well-defined focus of mild atrophy (arrows) in the sublingual salivary gland. Female rat exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

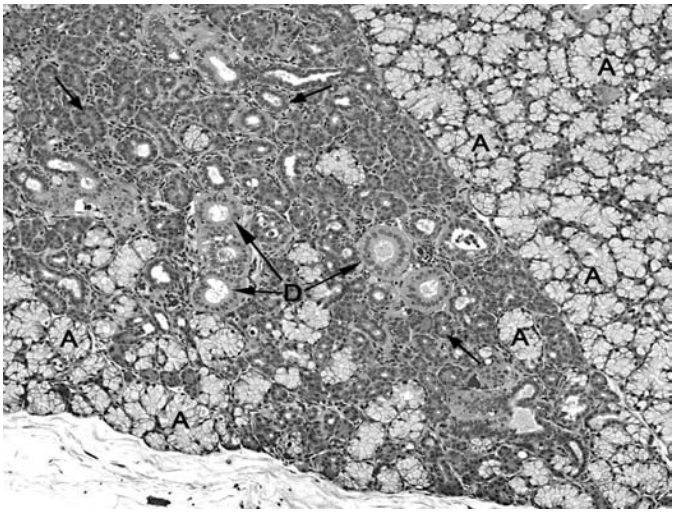


PLATE 12
Higher magnification of Plate 11. Histologically normal salivary gland acini (A) are located at the right of the panel and within the atrophic focus. The atrophic acini (arrows) have lost the pale secretory material that is clearly evident in the normal acini and are lined by low cuboidal epithelial cells. Salivary gland ducts (D). H&E

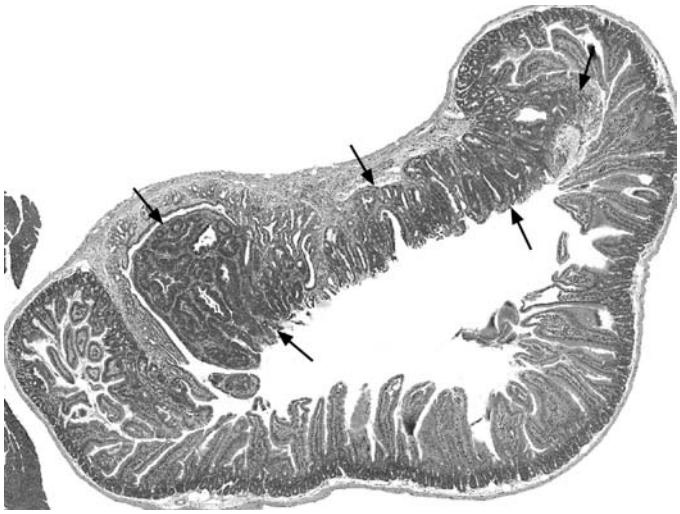


PLATE 13
Adenoma of the duodenum (arrows) that has distorted and replaced a focally extensive segment of the mucosa and protruded into the lumen. Normal mucosa is seen at either side of and opposite the adenoma. Female mouse exposed to 172 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

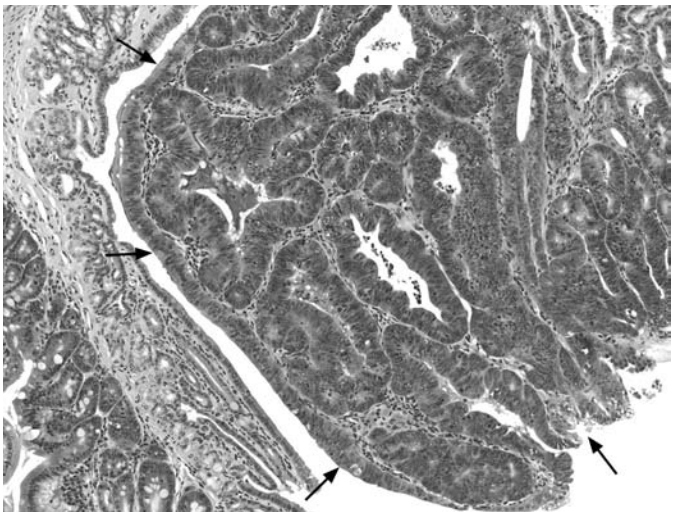


PLATE 14
Higher magnification of Plate 13 showing a portion of the adenoma composed of irregular glandular structures (arrows) lined by tall columnar, hyperchromatic epithelial cells with piling up of the cells in some areas. H&E

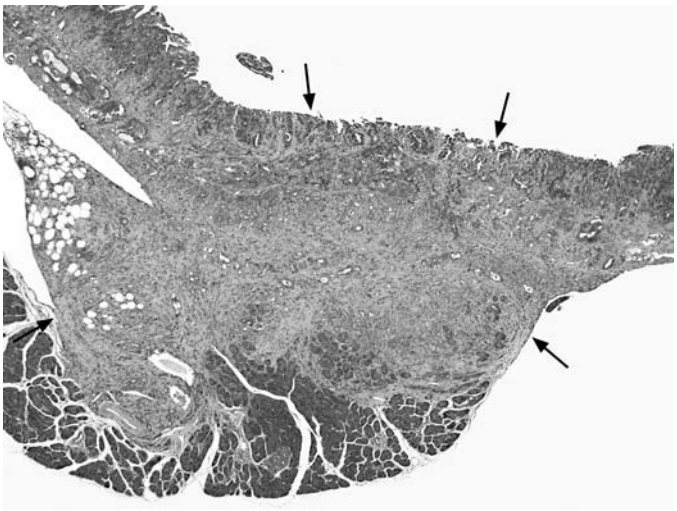


PLATE 15
Large carcinoma of the duodenum (arrows) that has effaced the mucosa invading the submucosa, muscle layers, and the pancreas. Male mouse exposed to 257.4 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

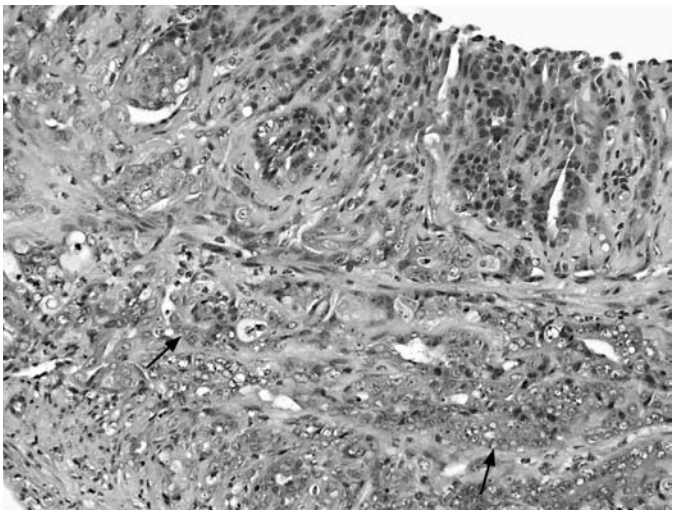


PLATE 16
Higher magnification of Plate 15 demonstrating dysplastic growth of atypical cells (arrows) and extensive fibroplasia. H&E

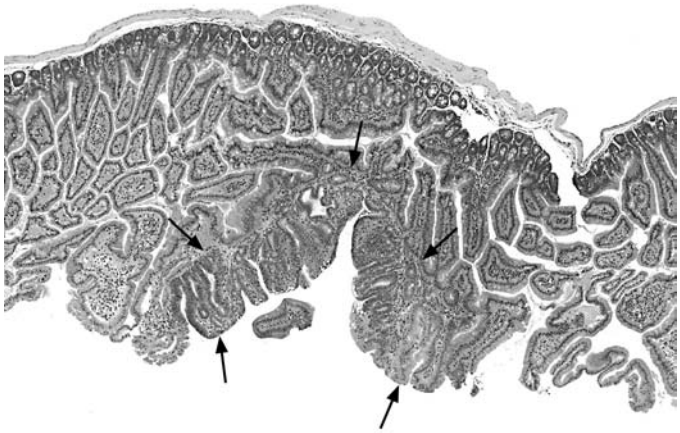


PLATE 17
Focal epithelial hyperplasia (arrows) occurring in the superficial mucosa of the duodenum. Female mouse exposed to 172 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

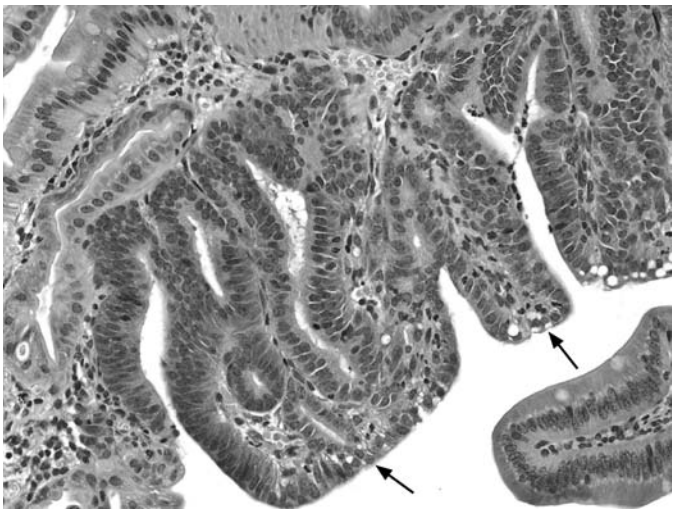


PLATE 18
Higher magnification of Plate 17. Villi are lined by increased numbers of tall columnar, hyperchromatic epithelial cells (arrows) that are similar to those in the adenomas. H&E

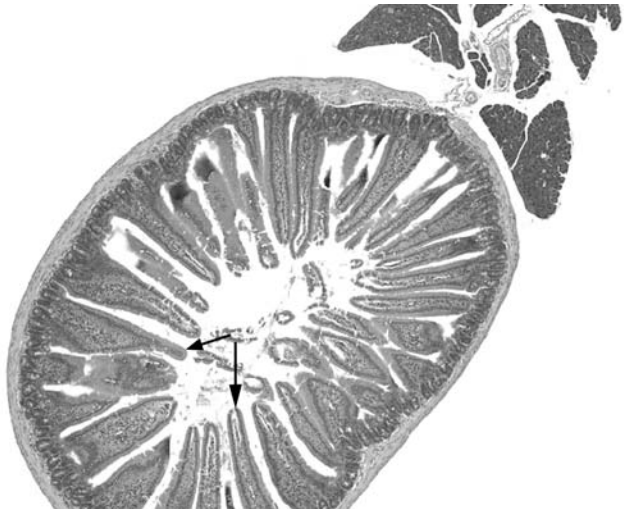


PLATE 19
Normal microscopic anatomy of the duodenum in a control female mouse in the 2-year drinking water study of sodium dichromate dihydrate. Note tall, slender villi (arrows) protruding into the lumen. H&E

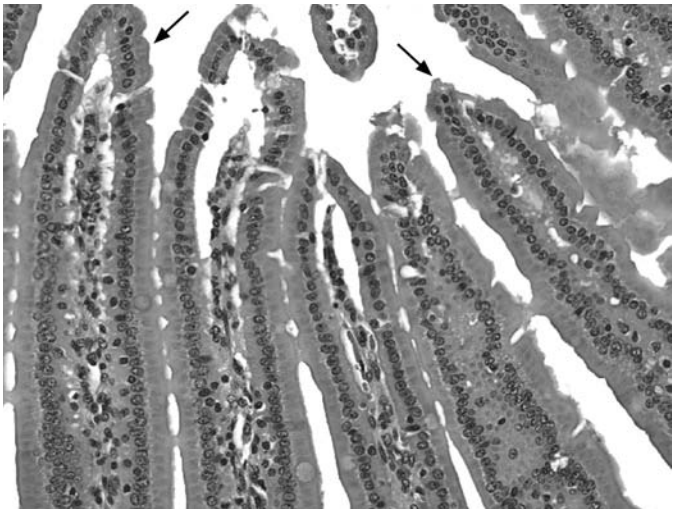


PLATE 20
Higher magnification of Plate 19. Duodenal villi (arrows) are tall and slender and lined by a single layer of tall columnar epithelial cells. H&E

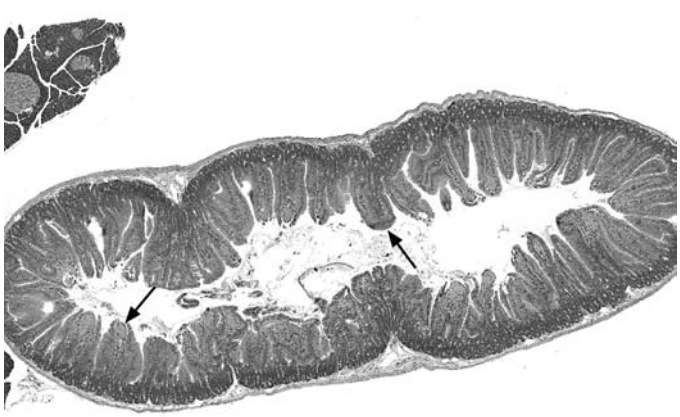


PLATE 21
Diffuse epithelial hyperplasia in the duodenum. Duodenal villi (arrows) are short, wide, and blunt. Female mouse exposed to 516 mg/L sodium dichromate dihydrate in drinking water for 2 years. H&E

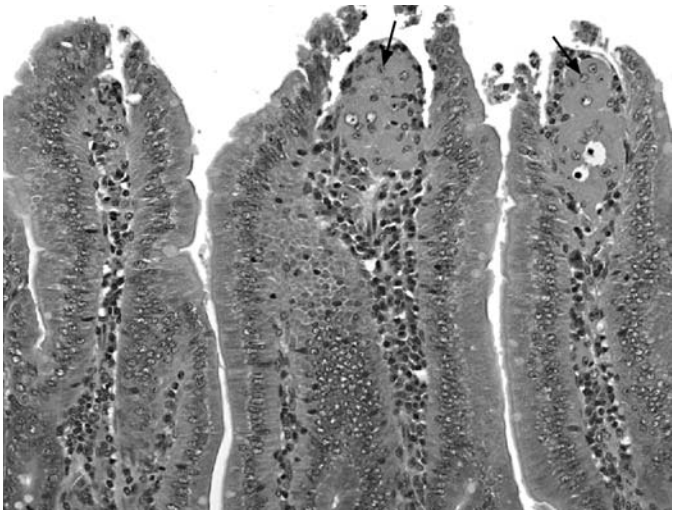


PLATE 22
Higher magnification of Plate 21. Note the hyperplastic epithelial cells extending along the villi with piling up in some areas. Note the histiocytes expanding the lamina propria at the tips of the villi (arrows). H&E

DISCUSSION AND CONCLUSIONS

Hexavalent chromium (Cr VI) was nominated for study because of its occurrence as a contaminant in drinking water source supplies and the potential for exposure of large populations of humans. Although Cr VI compounds are classified as human carcinogens following inhalation exposure (IARC, 1990; NTP, 1998), evidence regarding the carcinogenic potential of Cr VI compounds following exposure by other routes has been lacking. The results of 3-month toxicity studies of Cr VI administered in the drinking water to F344/N rats and B6C3F1, BALB/c, and *am3*-C57BL/6 mice as sodium dichromate dihydrate have been published (NTP, 2007a). Briefly, exposure to sodium dichromate dihydrate caused a microcytic hypochromic anemia in rats and mice, which was more severe in rats. The primary nonneoplastic lesions were observed in the glandular stomach of rats exposed to 1,000 mg/L and included focal ulceration, regenerative epithelial hyperplasia, and squamous epithelial metaplasia. Additional nonneoplastic lesions included histiocytic cellular infiltration in the duodenum of rats and mice, the liver of female rats, the mesenteric lymph nodes of mice, and the pancreatic lymph nodes of rats.

The 2-year studies presented in this Technical Report were designed after an NTP public meeting on hexavalent chromium held on July 24, 2002, at the National Institute of Environmental Health Sciences in Research Triangle Park, NC, to consider the results of the prechronic studies and recommendations from the panel of scientific experts convened at this meeting (NTP, 2006). Exposure concentrations for the 2-year studies were selected based on these public discussions and careful review of the data from the 3-month toxicity studies. Based on concentrations found in source waters, an additional low exposure group was added to the 2-year studies to provide a concentration that was closer to concentrations to which humans might be exposed through the drinking water. The lowest concentration of sodium dichromate dihydrate (14.3 mg/L) used in the current 2-year studies is equivalent to 5 mg/L chromium and is less than 10 times the reported hexavalent chromium concentration of 0.58 mg/L that was found in a groundwater monitoring well in Hinkley, CA (Pellerin and Booker, 2000). A wider spacing of exposures was also recommended to extend the exposure-response curve.

In the current 2-year studies, administration of sodium dichromate dihydrate in drinking water did not affect survival or produce clinical signs of toxicity in rats or mice of either sex. Significant exposure-related reductions in body weight gain and water consumption were observed for male and female rats and mice in the highest exposure groups. These effects were partly attributed to poor palatability of the dose formulations rather than direct toxicity from sodium dichromate dihydrate exposure. Lesions were not observed in the glandular stomach with increased duration of exposure in contrast to the 3-month studies, which used higher exposure concentrations.

Similar to the results from the 3-month toxicity studies in rats and mice, exposure-related erythrocyte microcytosis, hypochromia, and responsive anemia occurred in exposed rats. However, there was an amelioration of the effects by the 12-month time point, suggesting that the erythron effect was transient and resolved with time. The transient nature suggests an adaptive response by the exposed animals. The decreased red blood cell size and hypochromia is consistent with an ineffective erythropoiesis and could suggest some perturbation in iron metabolism and/or hemoglobin production. The mice were less affected compared to rats and had only a mild erythrocyte microcytosis. Similar hematological effects have been reported for rats and mice following oral exposure to Cr VI (Kumar and Barthwal, 1991; NTP, 1996a,b, 1997, 2007a; ATSDR, 2000). Hematological findings of reduced red blood cell, hematocrit, and hemoglobin values have also been reported in a 90-day inhalation toxicity study of soluble hexavalent chromium trioxide [CrO_3 (VI)] in male Sprague-Dawley rats (Kim *et al.*, 2004).

In the 3-month toxicity studies (NTP, 2007a) and in the current 2-year studies of sodium dichromate dihydrate, histiocytic cellular infiltration was consistently observed in several tissues including the liver, duodenum, and mesenteric and pancreatic lymph nodes of rats and mice.

The severities of these lesions were generally minimal to moderate and were characterized by the presence of individual, small clusters, and sometimes syncytia of macrophages. The significance of these lesions is not known.

In the 2-year rat study, increased incidences of neoplasms of the squamous epithelium that lines the oral mucosa and tongue were observed in male and female rats, indicating a neoplastic effect of sodium dichromate dihydrate exposure on epithelial tissues of the upper alimentary system (oral cavity). There were positive trends in the incidences of squamous cell carcinoma of the oral cavity in male and female rats. The incidences of squamous cell carcinoma of the oral mucosa in 516 mg/L males and females were significantly increased. Two females exposed to 172 mg/L also had squamous cell carcinoma of the oral mucosa. The incidences of squamous cell carcinoma of the oral mucosa in males and females exceeded the historical control ranges for drinking water studies and for all routes of administration. The oral mucosa carcinomas were highly aggressive neoplasms that originated in the oral mucosa of the palate and invaded the underlying submucosa, the soft tissue surrounding the nose, and in a few cases, the tongue, Harderian gland, and brain. A positive trend also occurred in males and females when incidences of papilloma and carcinoma of the oral mucosa or tongue were combined, and the incidences in the 516 mg/L groups were significantly increased. Nonneoplastic lesions were not observed in the oral mucosa. Because of the increased incidences of squamous cell neoplasms of the oral cavity in both male and female rats and the rarity of these neoplasms in historical controls, these neoplasms were considered to be clear evidence of carcinogenicity of sodium dichromate dihydrate exposure.

In contrast to rats, neoplasms in epithelial tissues of the lower alimentary system (small intestine) were observed in mice. The incidences of adenoma of the duodenum were significantly increased in males exposed to 257.4 mg/L and females exposed to 172 or 516 mg/L. The incidence of adenoma of the jejunum was significantly increased in females exposed to 516 mg/L. The incidence of carcinoma was significantly increased in the duodenum of 516 mg/L female mice. When adenomas and carcinomas were combined for all sites of the small intestine, including the duodenum, jejunum, and ileum, there was a clear exposure response relationship, and the incidences were statistically significant in the two highest exposure groups of male and female mice. In addition, low incidences of focal epithelial hyperplasia were observed in the duodenum and jejunum of male and female mice. Although not statistically significant, this lesion was considered a preneoplastic lesion related to chemical exposure because of the cytologic similarities to adenomas. The incidence of diffuse epithelial cell hyperplasia was also elevated in exposed male and female mice compared to the control groups. The background incidence of adenoma or carcinoma (combined) in the small intestine (all sites) of B6C3F1 mice is very low in NTP studies (Tables C3 and D3). For example, only one adenoma has been observed in the duodenum of 350 historical control female mice, and no adenomas have been observed in the jejunum of 299 historical control male or 350 female mice in drinking water studies. The combined incidences of adenoma and carcinoma in 57.3 mg/L female mice exceeded the historical control ranges. Based on these observations, the increased incidences of intestinal neoplasms were considered to be clear evidence of carcinogenicity of sodium dichromate dihydrate exposure. Only two other chemicals tested by the NTP, captan and *o*-nitrotoluene (NCI, 1977; NTP, 2002), have caused increased incidences of neoplasms in the intestines of male or female mice; neither of these chemicals were administered in the drinking water. The 2-year study of captan (NCI, 1977) is the only other study performed by the NTP in B6C3F1 mice in which both benign and malignant intestinal neoplasms of epithelial origin have been definitely attributed to chemical exposure (Shackelford and Elwell, 1999).

The lower body weights observed in male and female rats and mice exposed to the two highest exposure concentrations were partly attributed to poor palatability of the dosed water and consequent reductions in water consumption. However, several lines of evidence suggest that the animals were not dehydrated. When water consumption is adjusted for body weight (data not shown), dosed male and female rats and female mice drank approximately the same quantities of water per gram of body weight as the controls after the first 20 weeks on study. Male mice exposed to 257.4 mg/L drank less water per gram of body weight than did the controls throughout the study. Although mean body weights and water consumption were reduced in the higher exposure concentration groups, the average daily doses (mg sodium dichromate dihydrate per kilogram body weight) were in the same proportions as the drinking water concentrations (mg/L) for male and female rats and mice. Clinical observations related to dehydration including loss of skin turgor, dry mucous membranes,

retraction of eyes, hypoactivity, and poor hair coats were not observed in rats or mice in the 2-year studies of sodium dichromate dihydrate. Abnormalities in hematology and clinical chemistry parameters that typically indicate dehydration include increases in hematocrit, urine specific gravity, and serum concentrations of albumin, total protein, and urea nitrogen. In the current 2-year studies, hematology and clinical chemistry parameters were measured in male rats on days 4 and 22 and at months 3, 6, and 12. Significant decreases in hematocrit and serum concentrations of albumin and total protein were observed in males exposed to 516 mg/L. Taken together, these data suggest that the neoplastic and nonneoplastic effects of sodium dichromate dihydrate were not associated with dehydration.

There are few human or animal studies in the literature reporting the potential effects of Cr VI following oral exposure. However, inhalation exposure to Cr VI compounds has been shown to affect the gastrointestinal system in humans resulting in stomach pain, gastritis, and stomach and intestinal ulceration (ATSDR, 2000). Oral exposure also occurs after inhalation of chromium compounds due to mucociliary clearance and subsequent swallowing of particulates. Although lung cancer related to chromium exposure is well documented, there are conflicting reports in the literature (reviewed by Cohen *et al.*, 1993; Costa 1997; ATSDR, 2000; Proctor *et al.*, 2002; Costa and Klein 2006; Sedman *et al.*, 2006) regarding the occurrence of other types of cancer attri-buted to chromium exposure. Cohen *et al.* (1993) reported that increased incidences of stomach cancer were seen in numerous epidemiological studies; excesses of kidney, prostate gland, and bladder cancers were also seen in workers exposed to Cr VI. Costa (1997) compiled standardized mortality ratios from several studies that showed increased incidences of lymphoma and leukemia and cancers of the prostate gland, stomach, bladder, brain, and genital system in workers occupationally exposed to chromium. Only one epidemiology study has specifically addressed human exposure to Cr VI in drinking water (Zhang and Li, 1987); these authors reported increased incidences of lung and stomach tumors in a population consuming water contaminated by a nearby chromium ore smelting facility, although chromium exposure was likely by multiple routes (inhalation, drinking water, food, and soil). Similar to the results observed in the current 2-year rat study, occupational exposure to Cr VI in the electroplating industry may also be associated with oral cavity cancer, based on the diagnosis of oral cavity papillomas in employees of chromium electroplating factories in Czechoslovakia (ATSDR, 2000). While some reports described above suggest that Cr VI is a potential human carcinogen via the oral route of exposure, the USEPA (1998) and IARC (1990) concluded that there was insufficient data to make this determination. A review of human and animal data by Proctor *et al.* (2002) concluded that Cr VI is not carcinogenic in humans at permissible drinking water concentrations.

Nevertheless, based on the studies reviewed above, neoplasms in the oral cavity and stomach might be expected in animal carcinogenesis studies. In the current studies, oral cavity neoplasms were only observed in F344/N rats. Of 21 chemicals that have caused neoplasms of the oral cavity in NTP studies, none produced these neoplasms in male mice and only one, 1,2,3-trichloropropane, (NTP, 1993) produced oral cavity neoplasms in female mice. These results demonstrate the greater sensitivity of the oral cavity of rats to chemical-induced neoplasms compared to mice. Only one other lifetime animal carcinogenicity study was identified, in which Cr VI was administered in the drinking water as potassium chromate to three generations of NMRI mice (Borneff *et al.*, 1968). In treated mice, two of 66 females exposed to 9 mg Cr VI/kg developed forestomach carcinoma compared with none of the control mice. This difference was not statistically significant. However, when benign (9/66 papillomas) and malignant (2/66 carcinomas) forestomach neoplasms were combined in three generations of female mice, there was a statistically significant increase compared to the control group (2/79) (Sedman *et al.*, 2006). This study had several limitations including the use of only one exposure concentration of Cr VI and high early mortality in the F_0 generation as a result of ectromelia (mousepox) virus.

It has been hypothesized that oral exposure to Cr VI would not produce an increase in cancer, except perhaps in the stomach, due to the efficient reducing capacity of the stomach (De Flora *et al.*, 1997; De Flora, 2000; Proctor *et al.*, 2002). Notably, no neoplasms or nonneoplastic lesions were observed in the forestomach or glandular stomach of rats or mice. However, the exposure-related increases in the incidences of neoplasms in the duodenum and jejunum of mice in the current 2-year study suggests that under the conditions of this study, a portion of the administered Cr VI exited the stomach unreduced and exerted a carcinogenic effect on the proximal segments of the small intestine in mice. Differences in the oral toxicities of hexavalent

and trivalent chromium (Cr III) in animal studies provide additional evidence that hexavalent chromium is not completely converted to trivalent chromium in the stomach (ATSDR, 2000).

As part of the 2-year studies, total chromium content in excreta and selected tissues was determined in additional groups of male rats and female mice (Appendix J). Since hexavalent chromium as chromate structurally resembles sulfate and phosphate, it can be taken up by all cells and organs throughout the body (Costa, 1997). Chromate and dichromate are in equilibrium in aqueous solutions, so both forms will be present regardless of the form initially provided. Animals were removed from sodium dichromate dihydrate exposure, and urine and feces were collected for 2 days before the time of tissue collection. Animals were euthanized, and erythrocytes, plasma, forestomach, glandular stomach, liver, and kidney were removed for total chromium analysis. Current analytical procedures can not differentiate between the oxidation states of chromium in biological tissues. However, the speciation of absorbed chromium can be inferred from studies comparing Cr VI and Cr III based on the relative pattern of partitioning and retention of total chromium in the erythrocytes and tissues compared to plasma. Cr VI is transported into the erythrocytes and tissues, while Cr III remains in blood plasma because it is not a substrate for transport (Proctor *et al.*, 2002).

Significantly increased tissue concentrations of total chromium were observed in the erythrocytes, liver, kidney, forestomach, and glandular stomach of exposed rats and mice compared to controls indicating that additional Cr VI absorption occurs in these tissues, where it appears to accumulate with exposure concentration and time (Tables J1 and J2). The tissue concentrations of chromium were higher than would be expected based only on the presence of erythrocytes in the blood of these tissues. Additional studies have been conducted by the NTP to analyze the concentrations of chromium in similar tissues following Cr III administration in the diet as chromium picolinate monohydrate, a dietary supplement designed to increase Cr III absorption (Figure 7). Taken together, these studies demonstrate that at equivalent chromium exposures there were significantly increased concentrations of chromium in each tissue when the chromium was administered as Cr VI, compared to when the chromium was administered as Cr III. For example, at 25 weeks, chromium concentrations in these tissues were 5 to 16 times higher in animals administered chromium as Cr VI than in animals administered chromium as Cr III. In the current studies, the small intestine was not collected for total chromium analysis. However, other reports suggest that hexavalent chromium is also likely to be absorbed in the small intestine to a greater extent than trivalent chromium. Infusion of trivalent chromium into the duodenum or jejunum resulted in 1% to 2% of the dose being absorbed in humans or 1% to 4% in rats, whereas infusion of hexavalent chromium resulted in marked increases in absorption in humans and rats (Donaldson and Barreras, 1966; Febel *et al.*, 2001).

The tissue distribution data are consistent with those reported in the literature where tissue concentrations of chromium were reported following 11 months of exposure in male and female rats given chromium in the drinking water at 25 mg/L in both hexavalent and trivalent forms (Costa, 1997; Costa and Klein, 2006). In these studies, concentrations of chromium in the liver, kidney, and bone were 5.7, 12.0, and 6.4 µg/g, respectively, in rats administered hexavalent chromium as potassium chromate and 0.38, 1.6, and 0.36 µg/g, respectively, in rats administered trivalent chromium as chromium trichloride. The authors concluded that a significant amount of Cr VI escapes reduction in the red blood cells and stomach. The study by Davidson *et al.* (2004) demonstrating increased susceptibility to skin cancer induction in hairless mice following coexposure to ultraviolet light and Cr VI in the drinking water provides additional evidence that Cr VI can have systemic effects that are distant from the site of exposure.

The postulated mechanism(s) underlying chromium-induced genotoxicity and carcinogenicity is the subject of much research and some debate. Cr VI readily enters cells via nonspecific anion channels, in contrast to Cr III which cannot easily pass through the cell membrane (IARC, 1990). Cr VI has been postulated by a number of authors to exert its genotoxic effects, in part, through the generation of oxygen radicals (Sugden *et al.*, 1990; Sugiyama, 1992; Kasprzak, 1995; Shi *et al.*, 1999; Vaglenov *et al.*, 1999; Benova *et al.*, 2002; O'Brien *et al.*, 2003) during intracellular reduction from the hexavalent form through the more reactive Cr V and Cr IV valences to Cr III. It has been suggested that both enzymatic and nonenzymatic pathways may be involved in chromium reduction, although at normal physiological

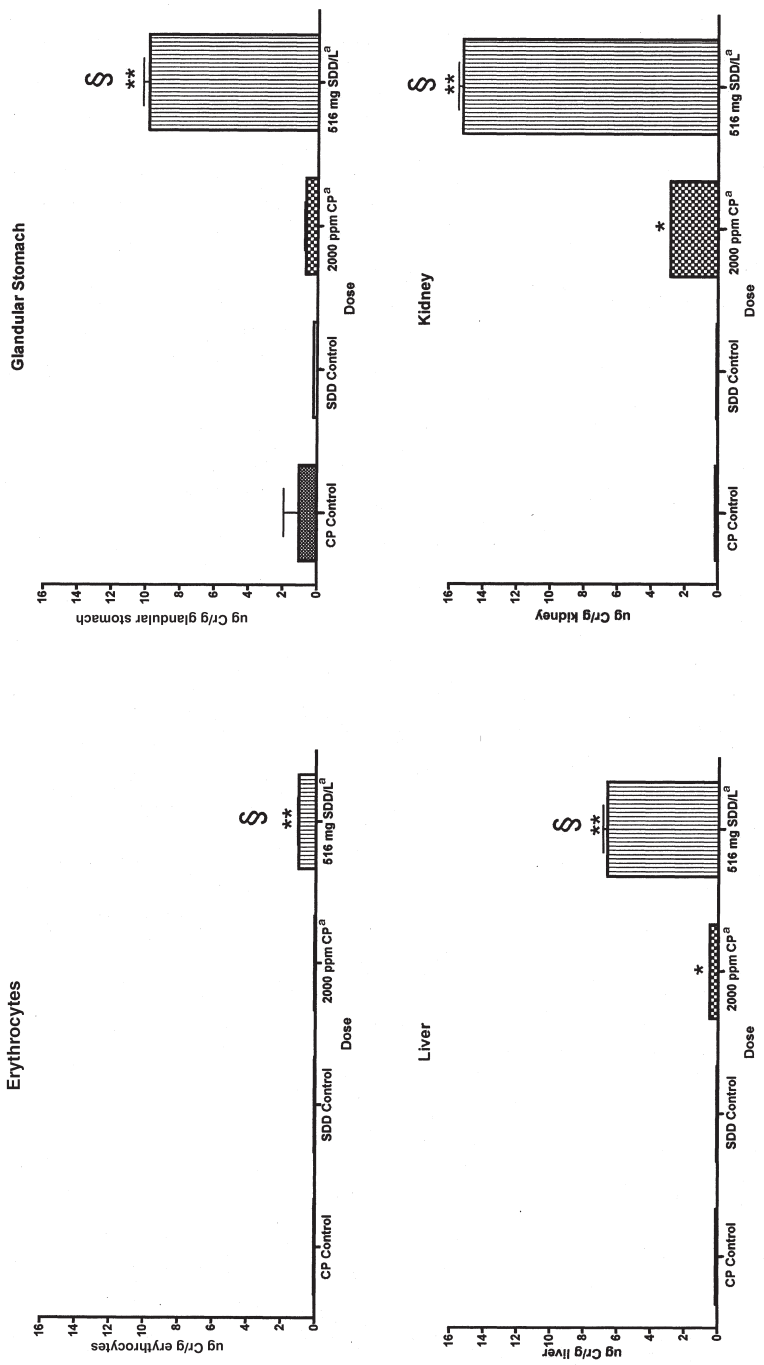


FIGURE 7
Comparison of Chromium (Cr) Concentrations on Day 182 in Male Rat Tissues Following Oral Administration as Cr III or Cr VI

* P<0.05 compared to corresponding control group

** P<0.01

§ P<0.001 compared to corresponding chromium picolinate (CP) dose group

[a] The NTP conducted two studies of Cr, a 2-year bioassay of CP monohydrate in feed (NTP, 2008) and the current 2-year bioassay of sodium dichromate dihydrate (SDD) in drinking water. To provide a basis of comparison between the two studies, exposure concentrations were converted to mg Cr/kg body weight using the food and water consumption data for weeks 1 to 25 of each study. The lowest exposure concentration used in the CP study was 2,000 ppm and 15.2 mg Cr/kg body weight. The comparable exposure concentration used in the SDD study was 516 mg/L and 8.95 mg Cr/kg body weight.

conditions, nonenzymatic reduction is believed to dominate (De Flora *et al.*, 1990; Standeven and Wetterhahn, 1991a). The primary reductants of Cr VI are ascorbic acid, glutathione, and cysteine, with ascorbic acid being the main reductant. During reduction of Cr VI to Cr III, it has been suggested that formation of reactive carbon-based radical species may result in DNA strand breakage and other types of damage (reviewed by O'Brien *et al.*, 2003). Although there are numerous studies providing experimental evidence in support of the role of reactive oxygen species in the genotoxicity of chromium (Chorvatovicova *et al.*, 1991, 1993; Sarkar *et al.*, 1993; Pattison *et al.*, 2001; Cemeli *et al.*, 2003), other studies raise questions about the relative contribution of this mechanism (O'Brien *et al.*, 2003; Zhitkovich, 2005; Quievryn *et al.*, 2006).

Cr III, the final product of intracellular reduction of Cr VI, has been shown to interact directly with DNA and other macromolecules to induce chromosomal alterations and mutational changes (Zhitkovich *et al.*, 2001, 2002; O'Brien *et al.*, 2003; Quievryn *et al.*, 2003, 2006; Zhitkovich, 2005; Reynolds *et al.*, 2007). The availability of intracellular ascorbate for Cr VI reduction may be directly related to the amount of Cr-induced DNA damage observed (Standeven and Wetterhahn, 1991b; Quievryn *et al.*, 2006; Reynolds *et al.*, 2007). DNA adducts, DNA-protein crosslinks, and DNA-interstrand crosslinks have all been identified as products of Cr III-DNA interactions. Detailed discussions of the types of Cr-DNA adducts that are formed *in vivo* and *in vitro*, along with the biological consequences of these adducts, including mutagenicity, DNA replication inhibition, and cytotoxicity, and the DNA repair pathways that may be invoked in response to these kinds of damage, have recently been provided (O'Brien *et al.*, 2003; Zhitkovich, 2005). The relative contributions of the multiple, complex pathways of chromium-induced genotoxicity are not yet fully understood and continue to be investigated.

In summary, administration of sodium dichromate dihydrate in the drinking water to F344/N rats and B6C3F1 mice for 2 years resulted in increased incidences of epithelial neoplasms in the alimentary system of male and female rats and mice. There were increased incidences of neoplasms of the oral cavity (oral mucosa and tongue) in rats and exposure concentration-related increased incidences of adenoma and carcinoma of the small intestine in mice. Histiocytic cellular infiltration was observed in the small intestine, liver, and pancreatic and mesenteric lymph nodes of rats and mice. There was evidence of systemic exposure to Cr VI following oral administration in the drinking water based on the tissue distribution data, toxicity to the hematopoietic system, and the presence of microscopic changes in multiple tissues.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *clear evidence of carcinogenic activity** of sodium dichromate dihydrate in male and female F344/N rats based on increased incidences of squamous cell neoplasms of the oral cavity. There was *clear evidence of carcinogenic activity* of sodium dichromate dihydrate in male and female B6C3F1 mice based on increased incidences of neoplasms of the small intestine (duodenum, jejunum, or ileum).

Exposure to sodium dichromate dihydrate resulted in histiocytic cellular infiltration in the liver, small intestine, and pancreatic and mesenteric lymph nodes of rats and mice and diffuse epithelial hyperplasia in the small intestine of male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 14.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM DICHROMATE DIHYDRATE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	16	15	16	9	16
Natural deaths	6	5	3	5	4
Survivors					
Terminal sacrifice	28	30	30	36	29
Missing			1		1
Animals examined microscopically	50	50	49	50	49
Alimentary System					
Intestine large, cecum	(45)	(48)	(46)	(47)	(48)
Lipoma				1 (2%)	
Intestine large, colon	(47)	(49)	(49)	(48)	(48)
Leiomyosarcoma					1 (2%)
Intestine small, duodenum	(48)	(48)	(47)	(46)	(48)
Intestine small, ileum	(45)	(46)	(46)	(45)	(47)
Intestine small, jejunum	(44)	(47)	(45)	(46)	(46)
Leiomyoma		1 (2%)			
Leiomyosarcoma		1 (2%)			
Leiomyosarcoma, metastatic, intestine, large, colon					1 (2%)
Liver	(50)	(50)	(49)	(50)	(49)
Hepatocellular adenoma		1 (2%)	2 (4%)		1 (2%)
Leiomyosarcoma, metastatic, spleen					1 (2%)
Mesentery	(12)	(4)	(15)	(14)	(15)
Hemangioma					1 (7%)
Oral mucosa	(50)	(50)	(49)	(50)	(49)
Squamous cell carcinoma					6 (12%)
Squamous cell papilloma					1 (2%)
Pancreas	(50)	(50)	(49)	(50)	(49)
Mixed tumor benign				1 (2%)	
Acinus, adenoma	1 (2%)	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Acinus, adenoma, multiple			2 (4%)		1 (2%)
Salivary glands	(50)	(50)	(49)	(49)	(49)
Schwannoma malignant, metastatic, peripheral nerve					1 (2%)
Stomach, forestomach	(50)	(50)	(49)	(50)	(49)
Stomach, glandular	(50)	(50)	(49)	(50)	(49)
Lipoma	1 (2%)				1 (2%)
Tongue	(49)	(50)	(47)	(49)	(48)
Squamous cell carcinoma		1 (2%)			
Squamous cell papilloma					1 (2%)
Tooth				(1)	(4)
Squamous cell carcinoma, metastatic, oral mucosa					1 (25%)
Cardiovascular System					
Blood vessel		(4)			(3)
Heart	(50)	(50)	(49)	(50)	(49)
Schwannoma benign					1 (2%)
Schwannoma malignant				1 (2%)	1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Endocrine System					
Adrenal cortex	(50)	(50)	(49)	(50)	(49)
Adenoma				1 (2%)	
Adrenal medulla	(49)	(50)	(49)	(50)	(49)
Pheochromocytoma benign	5 (10%)	13 (26%)	10 (20%)	4 (8%)	3 (6%)
Pheochromocytoma malignant	1 (2%)		2 (4%)	3 (6%)	1 (2%)
Bilateral, pheochromocytoma benign	1 (2%)		4 (8%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)	(49)
Adenoma	4 (8%)	6 (12%)	3 (6%)	7 (14%)	5 (10%)
Adenoma, multiple		1 (2%)			
Carcinoma			1 (2%)		
Parathyroid gland	(46)	(46)	(46)	(49)	(48)
Adenoma					1 (2%)
Pituitary gland	(50)	(50)	(49)	(50)	(49)
Pars distalis, adenoma	15 (30%)	19 (38%)	19 (39%)	10 (20%)	16 (33%)
Pars distalis, adenoma, multiple	1 (2%)		1 (2%)		
Pars intermedia, adenoma			1 (2%)		
Thyroid gland	(50)	(50)	(49)	(50)	(49)
C-cell, adenoma	5 (10%)	6 (12%)	3 (6%)	7 (14%)	7 (14%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Follicular cell, carcinoma				1 (2%)	3 (6%)
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(49)
Preputial gland	(50)	(50)	(49)	(50)	(49)
Adenoma	4 (8%)	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Carcinoma	1 (2%)	4 (8%)	7 (14%)	3 (6%)	2 (4%)
Prostate	(50)	(50)	(49)	(50)	(49)
Adenoma	2 (4%)		2 (4%)		1 (2%)
Seminal vesicle	(50)	(50)	(49)	(50)	(49)
Testes	(50)	(50)	(49)	(50)	(49)
Bilateral, interstitial cell, adenoma	41 (82%)	34 (68%)	32 (65%)	39 (78%)	35 (71%)
Interstitial cell, adenoma	7 (14%)	10 (20%)	11 (22%)	10 (20%)	7 (14%)
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(49)
Lymph node	(14)	(7)	(6)	(11)	(9)
Deep cervical, carcinoma, metastatic, thyroid gland					1 (11%)
Lymph node, mandibular			(5)	(2)	(2)
Lymph node, mesenteric	(49)	(50)	(49)	(50)	(49)
Lymph node, pancreatic	(32)	(34)	(34)	(36)	(33)
Spleen	(50)	(50)	(49)	(50)	(49)
Hemangiosarcoma				1 (2%)	
Leiomyosarcoma					1 (2%)
Thymus	(48)	(50)	(46)	(49)	(47)
Thymoma malignant				1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Integumentary System					
Mammary gland	(50)	(49)	(48)	(50)	(49)
Carcinoma	1 (2%)				1 (2%)
Fibroadenoma	2 (4%)	2 (4%)	6 (13%)	3 (6%)	1 (2%)
Fibroadenoma, multiple			1 (2%)		
Skin	(50)	(50)	(49)	(50)	(49)
Basal cell adenoma	2 (4%)	3 (6%)		1 (2%)	1 (2%)
Basal cell carcinoma		2 (4%)	2 (4%)		
Keratoacanthoma	2 (4%)	3 (6%)	1 (2%)	4 (8%)	1 (2%)
Squamous cell carcinoma	1 (2%)				
Squamous cell papilloma	1 (2%)			1 (2%)	1 (2%)
Trichoepithelioma			1 (2%)		
Sebaceous gland, adenoma				1 (2%)	
Subcutaneous tissue, fibroma	7 (14%)	11 (22%)	13 (27%)	7 (14%)	7 (14%)
Subcutaneous tissue, fibroma, multiple	1 (2%)	1 (2%)		2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrous histiocytoma				1 (2%)	
Subcutaneous tissue, hemangioma	1 (2%)				
Subcutaneous tissue, lipoma		1 (2%)	1 (2%)		
Subcutaneous tissue, sarcoma	2 (4%)				
Subcutaneous tissue, schwannoma malignant, multiple		1 (2%)			
Musculoskeletal System					
Bone	(50)	(50)	(49)	(50)	(49)
Chordoma					1 (2%)
Osteosarcoma					1 (2%)
Skeletal muscle	(3)	(2)	(2)		(1)
Nervous System					
Brain	(50)	(50)	(49)	(50)	(49)
Astrocytoma malignant		1 (2%)			
Peripheral nerve	(4)	(6)	(5)	(2)	(5)
Schwannoma malignant					1 (20%)
Spinal cord	(4)	(6)	(5)	(2)	(5)
Respiratory System					
Lung	(50)	(50)	(49)	(50)	(49)
Alveolar/bronchiolar adenoma	3 (6%)	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)				
Alveolar/bronchiolar carcinoma			1 (2%)		1 (2%)
Basal cell carcinoma, metastatic, skin		1 (2%)			
Carcinoma, metastatic, thyroid gland					1 (2%)
Chordoma, metastatic, uncertain primary site					1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)			
Osteosarcoma, metastatic, uncertain primary site					2 (4%)
Sarcoma, metastatic, skin	1 (2%)				
Sarcoma, metastatic, uncertain primary site		1 (2%)			
Nose	(50)	(50)	(49)	(50)	(49)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Special Senses System					
Eye	(50)	(50)	(49)	(50)	(49)
Squamous cell carcinoma, metastatic, oral mucosa					1 (2%)
Harderian gland	(50)	(50)	(49)	(50)	(49)
Squamous cell carcinoma, metastatic, oral mucosa					2 (4%)
Urinary System					
Kidney	(50)	(50)	(49)	(50)	(49)
Urinary bladder	(50)	(50)	(49)	(50)	(49)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(49)	(50)	(49)
Histiocytic sarcoma			1 (2%)		
Leukemia mononuclear	26 (52%)	18 (36%)	22 (45%)	17 (34%)	19 (39%)
Mesothelioma malignant	2 (4%)		2 (4%)	1 (2%)	
Neoplasm Summary					
Total animals with primary neoplasms[c]	50	48	49	50	49
Total primary neoplasms	143	151	162	137	142
Total animals with benign neoplasms	49	47	47	49	49
Total benign neoplasms	107	120	122	105	100
Total animals with malignant neoplasms	29	25	31	29	31
Total malignant neoplasms	36	31	40	32	42
Total animals with metastatic neoplasms	1	3			6
Total metastatic neoplasms	1	3			12
Total animals with malignant neoplasms of uncertain primary site		1			3

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

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	6/49 (12%)	13/50 (26%)	14/49 (29%)	5/50 (10%)	4/49 (8%)
Adjusted rate[b]	13.6%	31.1%	33.5%	11.2%	9.3%
Terminal rate[c]	3/28 (11%)	10/30 (33%)	9/30 (30%)	4/36 (11%)	4/29 (14%)
First incidence (days)	639	687	636	595	729 (T)
Poly-3 test[d]	P=0.018N	P=0.042	P=0.024	P=0.493N	P=0.386N
Adrenal Medulla: Malignant Pheochromocytoma					
Overall rate	1/49 (2%)	0/50 (0%)	2/49 (4%)	3/50 (6%)	1/49 (2%)
Adjusted rate	2.3%	0.0%	4.9%	6.8%	2.3%
Terminal rate	1/28 (4%)	0/30 (0%)	2/30 (7%)	2/36 (6%)	1/29 (3%)
First incidence (days)	729 (T)	—[e]	729 (T)	721	729 (T)
Poly-3 test	P=0.585	P=0.510N	P=0.476	P=0.309	P=0.758
Adrenal Medulla: Benign or Malignant Pheochromocytoma					
Overall rate	7/49 (14%)	13/50 (26%)	15/49 (31%)	7/50 (14%)	5/49 (10%)
Adjusted rate	15.9%	31.1%	35.9%	15.7%	11.6%
Terminal rate	4/28 (14%)	10/30 (33%)	10/30 (33%)	5/36 (14%)	5/29 (17%)
First incidence (days)	639	687	636	595	729 (T)
Poly-3 test	P=0.030N	P=0.076	P=0.027	P=0.606N	P=0.397N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	4/50 (8%)	3/50 (6%)	2/49 (4%)	1/50 (2%)	1/49 (2%)
Adjusted rate	9.0%	7.2%	4.9%	2.3%	2.3%
Terminal rate	3/28 (11%)	3/30 (10%)	2/30 (7%)	1/36 (3%)	1/29 (3%)
First incidence (days)	677	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.140N	P=0.538N	P=0.379N	P=0.181N	P=0.189N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	4/50 (8%)	3/50 (6%)	3/49 (6%)	1/50 (2%)	2/49 (4%)
Adjusted rate	9.0%	7.2%	7.4%	2.3%	4.7%
Terminal rate	3/28 (11%)	3/30 (10%)	3/30 (10%)	1/36 (3%)	2/29 (7%)
First incidence (days)	677	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.277N	P=0.538N	P=0.549N	P=0.181N	P=0.353N
Mammary Gland: Fibroadenoma					
Overall rate	2/50 (4%)	2/50 (4%)	7/49 (14%)	3/50 (6%)	1/49 (2%)
Adjusted rate	4.5%	4.8%	17.1%	6.8%	2.3%
Terminal rate	1/28 (4%)	1/30 (3%)	6/30 (20%)	3/36 (8%)	1/29 (3%)
First incidence (days)	689	559	652	729 (T)	729 (T)
Poly-3 test	P=0.182N	P=0.674	P=0.059	P=0.496	P=0.512N
Mammary Gland: Fibroadenoma or Carcinoma					
Overall rate	3/50 (6%)	2/50 (4%)	7/49 (14%)	3/50 (6%)	2/49 (4%)
Adjusted rate	6.8%	4.8%	17.1%	6.8%	4.6%
Terminal rate	2/28 (7%)	1/30 (3%)	6/30 (20%)	3/36 (8%)	1/29 (3%)
First incidence (days)	689	559	652	729 (T)	667
Poly-3 test	P=0.279N	P=0.525N	P=0.124	P=0.659	P=0.513N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Oral Cavity (Oral Mucosa): Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	6/49 (12%)
Adjusted rate	0.0%	0.0%	0.0%	0.0%	13.6%
Terminal rate	0/28 (0%)	0/30 (0%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First incidence (days)	—	—	—	—	543
Poly-3 test	P<0.001	—[f]	—	—	P=0.015
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	1/50 (2%)	0/49 (0%)	0/50 (0%)	6/49 (12%)
Adjusted rate	0.0%	2.4%	0.0%	0.0%	13.6%
Terminal rate	0/28 (0%)	1/30 (3%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First incidence (days)	—	729 (T)	—	—	543
Poly-3 test	P<0.001	P=0.487	—	—	P=0.015
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	1/50 (2%)	0/49 (0%)	0/50 (0%)	7/49 (14%)
Adjusted rate	0.0%	2.4%	0.0%	0.0%	15.7%
Terminal rate	0/28 (0%)	1/30 (3%)	0/30 (0%)	0/36 (0%)	1/29 (3%)
First incidence (days)	—	729 (T)	—	—	543
Poly-3 test	P<0.001	P=0.487	—	—	P=0.007
Pancreas: Adenoma					
Overall rate	1/50 (2%)	2/50 (4%)	6/49 (12%)	2/50 (4%)	2/49 (4%)
Adjusted rate	2.3%	4.8%	14.6%	4.5%	4.7%
Terminal rate	1/28 (4%)	1/30 (3%)	5/30 (17%)	2/36 (6%)	2/29 (7%)
First incidence (days)	729 (T)	706	560	729 (T)	729 (T)
Poly-3 test	P=0.468N	P=0.478	P=0.044	P=0.498	P=0.489
Pancreatic Islets: Adenoma					
Overall rate	4/50 (8%)	7/50 (14%)	3/49 (6%)	7/50 (14%)	5/49 (10%)
Adjusted rate	8.9%	16.7%	7.4%	15.8%	11.4%
Terminal rate	2/28 (7%)	5/30 (17%)	3/30 (10%)	6/36 (17%)	3/29 (10%)
First incidence (days)	666	687	729 (T)	692	595
Poly-3 test	P=0.550	P=0.222	P=0.552N	P=0.254	P=0.486
Pancreatic Islets: Adenoma or Carcinoma					
Overall rate	4/50 (8%)	7/50 (14%)	4/49 (8%)	7/50 (14%)	5/49 (10%)
Adjusted rate	8.9%	16.7%	9.8%	15.8%	11.4%
Terminal rate	2/28 (7%)	5/30 (17%)	3/30 (10%)	6/36 (17%)	3/29 (10%)
First incidence (days)	666	687	636	692	595
Poly-3 test	P=0.562N	P=0.222	P=0.595	P=0.254	P=0.486
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	16/50 (32%)	19/50 (38%)	20/49 (41%)	10/50 (20%)	16/49 (33%)
Adjusted rate	35.4%	44.4%	46.1%	22.7%	35.2%
Terminal rate	9/28 (32%)	16/30 (53%)	13/30 (43%)	10/36 (28%)	9/29 (31%)
First incidence (days)	639	477	503	729 (T)	557
Poly-3 test	P=0.251N	P=0.256	P=0.207	P=0.135N	P=0.580N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Preputial Gland: Adenoma					
Overall rate	4/50 (8%)	3/50 (6%)	3/49 (6%)	2/50 (4%)	3/49 (6%)
Adjusted rate	9.0%	7.2%	7.3%	4.5%	7.0%
Terminal rate	3/28 (11%)	1/30 (3%)	1/30 (3%)	2/36 (6%)	3/29 (10%)
First incidence (days)	677	652	652	729 (T)	729 (T)
Poly-3 test	P=0.495N	P=0.532N	P=0.543N	P=0.341N	P=0.519N
Preputial Gland: Carcinoma					
Overall rate	1/50 (2%)	4/50 (8%)	7/49 (14%)	3/50 (6%)	2/49 (4%)
Adjusted rate	2.3%	9.5%	17.0%	6.8%	4.7%
Terminal rate	1/28 (4%)	2/30 (7%)	5/30 (17%)	3/36 (8%)	2/29 (7%)
First incidence (days)	729 (T)	595	652	729 (T)	729 (T)
Poly-3 test	P=0.300N	P=0.163	P=0.022	P=0.303	P=0.489
Preputial Gland: Adenoma or Carcinoma					
Overall rate	4/50 (8%)	6/50 (12%)	8/49 (16%)	5/50 (10%)	5/49 (10%)
Adjusted rate	9.0%	14.2%	19.3%	11.3%	11.6%
Terminal rate	3/28 (11%)	3/30 (10%)	5/30 (17%)	5/36 (14%)	5/29 (17%)
First incidence (days)	677	595	652	729 (T)	729 (T)
Poly-3 test	P=0.464N	P=0.339	P=0.141	P=0.494	P=0.478
Skin: Keratoacanthoma					
Overall rate	2/50 (4%)	3/50 (6%)	1/49 (2%)	4/50 (8%)	1/49 (2%)
Adjusted rate	4.5%	7.2%	2.4%	9.0%	2.3%
Terminal rate	1/28 (4%)	1/30 (3%)	0/30 (0%)	3/36 (8%)	1/29 (3%)
First incidence (days)	587	636	503	549	729 (T)
Poly-3 test	P=0.375N	P=0.470	P=0.528N	P=0.336	P=0.514N
Skin: Squamous Cell Papilloma or Keratoacanthoma					
Overall rate	3/50 (6%)	3/50 (6%)	1/49 (2%)	5/50 (10%)	2/49 (4%)
Adjusted rate	6.7%	7.2%	2.4%	11.2%	4.7%
Terminal rate	1/28 (4%)	1/30 (3%)	0/30 (0%)	4/36 (11%)	2/29 (7%)
First incidence (days)	587	636	503	549	729 (T)
Poly-3 test	P=0.517N	P=0.632	P=0.334N	P=0.355	P=0.519N
Skin: Basal Cell Adenoma					
Overall rate	2/50 (4%)	3/50 (6%)	0/49 (0%)	1/50 (2%)	1/49 (2%)
Adjusted rate	4.5%	7.2%	0.0%	2.3%	2.3%
Terminal rate	2/28 (7%)	2/30 (7%)	0/30 (0%)	1/36 (3%)	1/29 (3%)
First incidence (days)	729 (T)	713	—	729 (T)	729 (T)
Poly-3 test	P=0.370N	P=0.471	P=0.257N	P=0.502N	P=0.511N
Skin: Trichoepithelioma or Basal Cell Adenoma					
Overall rate	2/50 (4%)	3/50 (6%)	1/49 (2%)	1/50 (2%)	1/49 (2%)
Adjusted rate	4.5%	7.2%	2.5%	2.3%	2.3%
Terminal rate	2/28 (7%)	2/30 (7%)	1/30 (3%)	1/36 (3%)	1/29 (3%)
First incidence (days)	729 (T)	713	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.314N	P=0.471	P=0.530N	P=0.502N	P=0.511N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Skin: Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma					
Overall rate	2/50 (4%)	5/50 (10%)	3/49 (6%)	1/50 (2%)	1/49 (2%)
Adjusted rate	4.5%	11.8%	7.4%	2.3%	2.3%
Terminal rate	2/28 (7%)	3/30 (10%)	3/30 (10%)	1/36 (3%)	1/29 (3%)
First incidence (days)	729 (T)	345	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.133N	P=0.198	P=0.461	P=0.502N	P=0.511N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma					
Overall rate	4/50 (8%)	3/50 (6%)	1/49 (2%)	5/50 (10%)	2/49 (4%)
Adjusted rate	8.9%	7.2%	2.4%	11.2%	4.7%
Terminal rate	1/28 (4%)	1/30 (3%)	0/30 (0%)	4/36 (11%)	2/29 (7%)
First incidence (days)	587	636	503	549	729 (T)
Poly-3 test	P=0.429N	P=0.539N	P=0.205N	P=0.496	P=0.358N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma					
Overall rate	5/50 (10%)	8/50 (16%)	4/49 (8%)	6/50 (12%)	3/49 (6%)
Adjusted rate	11.1%	18.7%	9.7%	13.4%	7.0%
Terminal rate	2/28 (7%)	4/30 (13%)	3/30 (10%)	5/36 (14%)	3/29 (10%)
First incidence (days)	587	345	503	549	729 (T)
Poly-3 test	P=0.180N	P=0.243	P=0.553N	P=0.495	P=0.381N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	8/50 (16%)	12/50 (24%)	13/49 (27%)	9/50 (18%)	8/49 (16%)
Adjusted rate	17.8%	28.0%	31.3%	20.2%	18.1%
Terminal rate	5/28 (18%)	8/30 (27%)	10/30 (33%)	8/36 (22%)	3/29 (10%)
First incidence (days)	652	584	617	595	609
Poly-3 test	P=0.225N	P=0.186	P=0.110	P=0.493	P=0.596
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma					
Overall rate	3/50 (6%)	1/50 (2%)	1/49 (2%)	1/50 (2%)	1/49 (2%)
Adjusted rate	6.7%	2.4%	2.4%	2.3%	2.3%
Terminal rate	1/28 (4%)	0/30 (0%)	0/30 (0%)	1/36 (3%)	1/29 (3%)
First incidence (days)	696	617	560	729 (T)	729 (T)
Poly-3 test	P=0.387N	P=0.327N	P=0.333N	P=0.308N	P=0.317N
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma					
Overall rate	11/50 (22%)	13/50 (26%)	14/49 (29%)	9/50 (18%)	9/49 (18%)
Adjusted rate	24.4%	30.1%	33.3%	20.2%	20.3%
Terminal rate	6/28 (21%)	8/30 (27%)	10/30 (33%)	8/36 (22%)	4/29 (14%)
First incidence (days)	652	584	560	595	609
Poly-3 test	P=0.165N	P=0.358	P=0.247	P=0.412N	P=0.418N
Testes: Adenoma					
Overall rate	48/50 (96%)	44/50 (88%)	43/49 (88%)	49/50 (98%)	42/49 (86%)
Adjusted rate	97.5%	93.8%	94.5%	99.7%	90.3%
Terminal rate	28/28 (100%)	29/30 (97%)	30/30 (100%)	36/36 (100%)	28/29 (97%)
First incidence (days)	484	454	501	520	543
Poly-3 test	P=0.101N	P=0.343N	P=0.404N	P=0.464	P=0.110N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Thyroid Gland (C-cell): Adenoma					
Overall rate	5/50 (10%)	6/50 (12%)	3/49 (6%)	7/50 (14%)	7/49 (14%)
Adjusted rate	11.2%	14.4%	7.3%	15.6%	16.2%
Terminal rate	4/28 (14%)	4/30 (13%)	0/30 (0%)	5/36 (14%)	6/29 (21%)
First incidence (days)	617	687	631	549	652
Poly-3 test	P=0.255	P=0.452	P=0.399N	P=0.383	P=0.356
Thyroid Gland (C-cell): Carcinoma					
Overall rate	1/50 (2%)	2/50 (4%)	1/49 (2%)	3/50 (6%)	2/49 (4%)
Adjusted rate	2.3%	4.8%	2.4%	6.8%	4.7%
Terminal rate	1/28 (4%)	2/30 (7%)	0/30 (0%)	3/36 (8%)	2/29 (7%)
First incidence (days)	729 (T)	729 (T)	640	729 (T)	729 (T)
Poly-3 test	P=0.439	P=0.477	P=0.743	P=0.303	P=0.489
Thyroid Gland (C-cell): Adenoma or Carcinoma					
Overall rate	6/50 (12%)	7/50 (14%)	4/49 (8%)	10/50 (20%)	9/49 (18%)
Adjusted rate	13.4%	16.8%	9.6%	22.2%	20.8%
Terminal rate	5/28 (18%)	5/30 (17%)	0/30 (0%)	8/36 (22%)	8/29 (28%)
First incidence (days)	617	687	631	549	652
Poly-3 test	P=0.163	P=0.447	P=0.414N	P=0.207	P=0.262
Thyroid Gland (Follicular Cell): Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/50 (2%)	3/49 (6%)
Adjusted rate	0.0%	0.0%	0.0%	2.3%	6.9%
Terminal rate	0/28 (0%)	0/30 (0%)	0/30 (0%)	1/36 (3%)	0/29 (0%)
First incidence (days)	—	—	—	729 (T)	605
Poly-3 test	P=0.007	—	—	P=0.499	P=0.116
All Organs: Mononuclear Cell Leukemia					
Overall rate	26/50 (52%)	18/50 (36%)	22/49 (45%)	17/50 (34%)	19/49 (39%)
Adjusted rate	52.6%	41.9%	47.5%	35.2%	42.1%
Terminal rate	9/28 (32%)	12/30 (40%)	11/30 (37%)	8/36 (22%)	10/29 (35%)
First incidence (days)	482	617	272	399	557
Poly-3 test	P=0.250N	P=0.204N	P=0.384N	P=0.060N	P=0.205N
All Organs: Benign Neoplasms					
Overall rate	49/50 (98%)	47/50 (94%)	47/49 (96%)	49/50 (98%)	49/49 (100%)
Adjusted rate	99.4%	99.4%	99.7%	99.7%	100.0%
Terminal rate	28/28 (100%)	30/30 (100%)	30/30 (100%)	36/36 (100%)	29/29 (100%)
First incidence (days)	484	454	501	520	543
Poly-3 test	P=0.859	P=0.998N	P=0.997	P=0.995	P=0.993
All Organs: Malignant Neoplasms					
Overall rate	29/50 (58%)	26/50 (52%)	31/49 (63%)	29/50 (58%)	33/49 (67%)
Adjusted rate	58.7%	56.3%	65.3%	60.0%	69.8%
Terminal rate	11/28 (39%)	15/30 (50%)	17/30 (57%)	20/36 (56%)	18/29 (62%)
First incidence (days)	482	337	272	399	543
Poly-3 test	P=0.129	P=0.491N	P=0.319	P=0.527	P=0.174

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
All Organs: Benign or Malignant Neoplasms					
Overall rate	50/50 (100%)	49/50 (98%)	49/49 (100%)	50/50 (100%)	49/49 (100%)
Adjusted rate	100.0%	99.8%	100.0%	100.0%	100.0%
Terminal rate	28/28 (100%)	30/30 (100%)	30/30 (100%)	36/36 (100%)	29/29 (100%)
First incidence (days)	482	337	272	399	543
Poly-3 test	P=1.000	P=1.000N	—	—	—

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

TABLE A3
Historical Incidence of Oral Cavity Neoplasms in Control Male F344/N Rats[a]

Study	Incidence in Controls	
	Oral Mucosa	All Sites[b]
	Squamous Cell Carcinoma	Papilloma, Squamous Cell Papilloma, or Squamous Cell Carcinoma
Historical Incidence: Drinking Water Studies		
Bromochloroacetic acid	0/50	0/50
Bromodichloromethane	0/50	1/50
Dibromoacetic acid	0/50	0/50
Dibromoacetonitrile	0/50	0/50
Dipropylene glycol	0/50	0/50
Sodium chlorate	0/50	0/50
Sodium dichromate dihydrate	0/50	—
Overall Historical Incidence: Drinking Water Studies		
Total	0/350	1/300 (0.3%)
Mean ± standard deviation		0.3% ± 0.8%
Range		(0%-2%)
Overall Historical Incidence: All Routes		
Total (%)	5/1,499 (0.3%)	10/1,449 (0.7%)
Mean ± standard deviation	0.3% ± 0.7%	0.6% ± 0.8%
Range	(0%-2%)	(0%-2%)

[a] Data as of March 5, 2007, with sodium dichromate dihydrate data added from Table A1
[b] All sites includes the oral mucosa, tongue, pharynx, tooth, and gingiva; sodium dichromate dihydrate data not included

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	16	15	16	9	16
Natural deaths	6	5	3	5	4
Survivors					
Terminal sacrifice	28	30	30	36	29
Missing			1		1
Animals examined microscopically	50	50	49	50	49
Alimentary System					
Intestine large, cecum	(45)	(48)	(46)	(47)	(48)
Edema		1 (2%)	1 (2%)	2 (4%)	2 (4%)
Erosion				1 (2%)	
Ulcer			1 (2%)		1 (2%)
Intestine large, colon	(47)	(49)	(49)	(48)	(48)
Edema	1 (2%)				
Infiltration cellular, lymphocyte					1 (2%)
Intestine small, duodenum	(48)	(48)	(47)	(46)	(48)
Erosion	1 (2%)			1 (2%)	
Infiltration cellular, histiocyte			6 (13%)	36 (78%)	47 (98%)
Ulcer		1 (2%)			
Intestine small, ileum	(45)	(46)	(46)	(45)	(47)
Hyperplasia	1 (2%)				
Lymphoid tissue, hyperplasia	10 (22%)	11 (24%)	9 (20%)	7 (16%)	10 (21%)
Intestine small, jejunum	(44)	(47)	(45)	(46)	(46)
Hyperplasia					1 (2%)
Epithelium, hyperplasia	1 (2%)				
Liver	(50)	(50)	(49)	(50)	(49)
Angiectasis	1 (2%)	1 (2%)			
Basophilic focus	22 (44%)	28 (56%)	29 (59%)	32 (64%)	30 (61%)
Clear cell focus	23 (46%)	19 (38%)	16 (33%)	29 (58%)	25 (51%)
Degeneration, cystic	7 (14%)	3 (6%)	2 (4%)		2 (4%)
Eosinophilic focus	10 (20%)	5 (10%)	4 (8%)	8 (16%)	9 (18%)
Fatty change	12 (24%)	10 (20%)	10 (20%)	8 (16%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)		3 (6%)		
Hemorrhage		2 (4%)	1 (2%)	4 (8%)	3 (6%)
Hepatodiaphragmatic nodule	5 (10%)	6 (12%)	6 (12%)	7 (14%)	10 (20%)
Infiltration cellular, histiocyte	1 (2%)		2 (4%)	5 (10%)	34 (69%)
Inflammation, chronic	19 (38%)	25 (50%)	21 (43%)	28 (56%)	26 (53%)
Mixed cell focus	11 (22%)	7 (14%)	5 (10%)	13 (26%)	10 (20%)
Necrosis	3 (6%)	3 (6%)		2 (4%)	1 (2%)
Regeneration	2 (4%)	2 (4%)			
Syncytial alteration					1 (2%)
Thrombosis	1 (2%)				
Bile duct, hyperplasia	47 (94%)	38 (76%)	33 (67%)	22 (44%)	15 (31%)
Centrilobular, necrosis	8 (16%)	1 (2%)	3 (6%)	2 (4%)	5 (10%)
Hepatocyte, hyperplasia, focal		1 (2%)			
Intima, vein, hyperplasia					1 (2%)
Kupffer cell, pigmentation	2 (4%)		1 (2%)		

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Alimentary System (continued)					
Mesentery	(12)	(4)	(15)	(14)	(15)
Accessory spleen	1 (8%)		1 (7%)	1 (7%)	1 (7%)
Hemorrhage					1 (7%)
Fat, necrosis	11 (92%)	3 (75%)	10 (67%)	12 (86%)	13 (87%)
Oral mucosa	(50)	(50)	(49)	(50)	(49)
Pancreas	(50)	(50)	(49)	(50)	(49)
Atrophy	25 (50%)	16 (32%)	24 (49%)	24 (48%)	31 (63%)
Cyst	9 (18%)	7 (14%)	9 (18%)	9 (18%)	12 (24%)
Acinus, cytoplasmic alteration			1 (2%)		3 (6%)
Acinus, hyperplasia, focal	6 (12%)	10 (20%)	9 (18%)	7 (14%)	9 (18%)
Salivary glands	(50)	(50)	(49)	(49)	(49)
Atrophy	3 (6%)	1 (2%)	2 (4%)	4 (8%)	3 (6%)
Necrosis			1 (2%)		2 (4%)
Duct, cyst		1 (2%)			
Stomach, forestomach	(50)	(50)	(49)	(50)	(49)
Edema	3 (6%)			3 (6%)	3 (6%)
Erosion				1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)		1 (2%)	1 (2%)
Ulcer	1 (2%)	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Epithelium, hyperplasia	1 (2%)	2 (4%)	2 (4%)	5 (10%)	1 (2%)
Stomach, glandular	(50)	(50)	(49)	(50)	(49)
Cyst					1 (2%)
Edema		1 (2%)		1 (2%)	
Erosion	8 (16%)	4 (8%)	6 (12%)	5 (10%)	2 (4%)
Hyperplasia	8 (16%)	4 (8%)	9 (18%)	12 (24%)	12 (24%)
Infiltration cellular, lymphocyte					1 (2%)
Ulcer	1 (2%)	3 (6%)	1 (2%)	1 (2%)	
Epithelium, glands, dilatation				1 (2%)	
Glands, dilatation	1 (2%)		1 (2%)		1 (2%)
Tongue	(49)	(50)	(47)	(49)	(48)
Fibrosis					1 (2%)
Hemorrhage	1 (2%)				1 (2%)
Hemorrhage, chronic					1 (2%)
Inflammation, chronic	2 (4%)	5 (50%)	6 (13%)	6 (12%)	3 (6%)
Epithelium, hyperplasia	2 (4%)			2 (4%)	1 (2%)
Vein, thrombosis					1 (2%)
Tooth				(1)	(4)
Malformation					1 (25%)
Cardiovascular System					
Blood vessel		(4)			(3)
Dilatation					1 (33%)
Heart	(50)	(50)	(49)	(50)	(49)
Cardiomyopathy	46 (92%)	44 (88%)	44 (90%)	45 (90%)	45 (92%)
Inflammation, chronic					1 (2%)
Thrombosis	5 (10%)	3 (6%)	1 (2%)	2 (4%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Endocrine System					
Adrenal cortex	(50)	(50)	(49)	(50)	(49)
Accessory adrenal cortical nodule	17 (34%)	18 (36%)	13 (27%)	17 (34%)	8 (16%)
Angiectasis	1 (2%)		1 (2%)	1 (2%)	
Degeneration, fatty	7 (14%)	10 (20%)	9 (18%)	7 (14%)	11 (22%)
Hyperplasia, focal	2 (4%)	1 (2%)	6 (12%)		3 (6%)
Hyperplasia, diffuse	1 (2%)		1 (2%)		
Hypertrophy	1 (2%)				
Hypertrophy, focal		2 (4%)		4 (8%)	4 (8%)
Necrosis		2 (4%)	1 (2%)	1 (2%)	1 (2%)
Adrenal medulla	(49)	(50)	(49)	(50)	(49)
Hyperplasia	12 (24%)	11 (22%)	17 (35%)	9 (18%)	14 (29%)
Islets, pancreatic	(50)	(50)	(49)	(50)	(49)
Hyperplasia	2 (4%)			1 (2%)	1 (2%)
Parathyroid gland	(46)	(46)	(46)	(49)	(48)
Hyperplasia					1 (2%)
Pituitary gland	(50)	(50)	(49)	(50)	(49)
Pars distalis, angiectasis	2 (4%)	3 (6%)	2 (4%)	5 (10%)	3 (6%)
Pars distalis, cyst	3 (6%)	4 (8%)	7 (14%)	5 (10%)	5 (10%)
Pars distalis, cytoplasmic alteration, focal	2 (4%)	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Pars distalis, hyperplasia		1 (2%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	12 (24%)	6 (12%)	12 (24%)	14 (28%)	11 (22%)
Pars intermedia, angiectasis	1 (2%)			1 (2%)	2 (4%)
Pars intermedia, cyst	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Pars intermedia, metaplasia, atypical		1 (2%)			
Pars intermedia, pars nervosa, metaplasia, atypical				1 (2%)	
Thyroid gland	(50)	(50)	(49)	(50)	(49)
Ultimobranchial cyst			1 (2%)		2 (4%)
C-cell, hyperplasia	11 (22%)	13 (26%)	18 (37%)	14 (28%)	5 (10%)
Follicle, cyst	1 (2%)	1 (2%)			2 (4%)
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(49)	(50)	(49)
Granuloma sperm	2 (4%)				1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)	2 (4%)	2 (4%)
Preputial gland	(50)	(50)	(49)	(50)	(49)
Cyst	1 (2%)	1 (2%)			1 (2%)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)		1 (2%)
Inflammation, chronic	16 (32%)	11 (22%)	13 (27%)	17 (34%)	16 (33%)
Prostate	(50)	(50)	(49)	(50)	(49)
Cyst			1 (2%)		
Inflammation, chronic	19 (38%)	17 (34%)	14 (29%)	8 (16%)	14 (29%)
Epithelium, hyperplasia	7 (14%)	11 (22%)	7 (14%)	7 (14%)	8 (16%)
Seminal vesicle	(50)	(50)	(49)	(50)	(49)
Inflammation, chronic				1 (2%)	
Testes	(50)	(50)	(49)	(50)	(49)
Germinal epithelium, atrophy	5 (10%)	4 (8%)	6 (12%)	4 (8%)	8 (16%)
Interstitial cell, hyperplasia	4 (8%)	5 (10%)	3 (6%)	4 (8%)	4 (8%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(49)
Hemorrhage	1 (2%)				
Hyperplasia	4 (8%)	12 (24%)	7 (14%)	7 (14%)	6 (12%)
Myelofibrosis	2 (4%)			1 (2%)	2 (4%)
Lymph node	(14)	(7)	(6)	(11)	(9)
Deep cervical, ectasia					2 (22%)
Deep cervical, hyperplasia, lymphoid					2 (22%)
Mediastinal, ectasia	2 (14%)	1 (14%)		1 (9%)	1 (11%)
Mediastinal, hemorrhage	1 (7%)	2 (29%)	1 (17%)	1 (9%)	1 (11%)
Mediastinal, hyperplasia, lymphoid	1 (7%)	1 (14%)	1 (17%)	3 (27%)	2 (22%)
Mediastinal, pigmentation			1 (17%)		
Lymph node, mandibular			(5)	(2)	(2)
Ectasia			1 (20%)	1 (50%)	2 (100%)
Lymph node, mesenteric	(49)	(50)	(49)	(50)	(49)
Hemorrhage	2 (4%)	7 (14%)	9 (18%)	8 (16%)	17 (35%)
Hyperplasia, lymphoid	1 (2%)	6 (12%)	2 (4%)	1 (2%)	
Infiltration cellular, histiocyte	13 (27%)	11 (22%)	30 (61%)	39 (78%)	41 (84%)
Lymph node, pancreatic	(32)	(34)	(34)	(36)	(33)
Congestion			1 (3%)		
Ectasia	1 (3%)	1 (3%)	1 (3%)		
Hemorrhage		3 (9%)	4 (12%)	2 (6%)	1 (3%)
Hyperplasia, lymphoid					1 (3%)
Infiltration cellular, histiocyte	17 (53%)	22 (65%)	17 (50%)	17 (47%)	25 (76%)
Pigmentation			1 (3%)	1 (3%)	
Spleen	(50)	(50)	(49)	(50)	(49)
Accessory spleen	1 (2%)		2 (4%)	1 (2%)	
Fibrosis	2 (4%)	3 (6%)	2 (4%)	1 (2%)	
Hematopoietic cell proliferation	18 (36%)	25 (50%)	20 (41%)	20 (40%)	16 (33%)
Hemorrhage			1 (2%)	1 (2%)	1 (2%)
Metaplasia, lipocyte	1 (2%)				
Necrosis	4 (8%)		4 (8%)	2 (4%)	
Pigmentation	3 (6%)	2 (4%)	1 (2%)		3 (6%)
Lymphoid follicle, atrophy	1 (2%)				
Lymphoid follicle, hyperplasia		1 (2%)			
Thymus	(48)	(50)	(46)	(49)	(47)
Atrophy		1 (2%)	1 (2%)		1 (2%)
Integumentary System					
Mammary gland	(50)	(49)	(48)	(50)	(49)
Hyperplasia	25 (50%)	17 (35%)	19 (40%)	11 (22%)	14 (29%)
Inflammation, granulomatous				1 (2%)	
Skin	(50)	(50)	(49)	(50)	(49)
Angiectasis				1 (2%)	1 (2%)
Cyst	1 (2%)			1 (2%)	
Cyst epithelial inclusion	5 (10%)	3 (6%)	2 (4%)	3 (6%)	6 (12%)
Edema			1 (2%)		
Hyperkeratosis	5 (10%)	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Epidermis, hyperplasia			1 (2%)	1 (2%)	

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Musculoskeletal System					
Bone	(50)	(50)	(49)	(50)	(49)
Cranium, osteopetrosis	1 (2%)		2 (4%)	1 (2%)	
Femur, osteopetrosis					1 (2%)
Skeletal muscle	(3)	(2)	(2)		(1)
Atrophy					1 (100%)
Nervous System					
Brain	(50)	(50)	(49)	(50)	(49)
Compression	7 (14%)	6 (12%)	9 (18%)	3 (6%)	3 (6%)
Hemorrhage	1 (2%)				
Hydrocephalus		1 (2%)			1 (2%)
Peripheral nerve	(4)	(6)	(5)	(2)	(5)
Atrophy		1 (17%)			
Spinal cord	(4)	(6)	(5)	(2)	(5)
Vacuolization cytoplasmic	1 (25%)				
Respiratory System					
Lung	(50)	(50)	(49)	(50)	(49)
Edema	1 (2%)				
Foreign body					1 (2%)
Hemorrhage	10 (20%)	7 (14%)	7 (14%)	6 (12%)	8 (16%)
Infiltration cellular, histiocyte	28 (56%)	27 (54%)	32 (65%)	29 (58%)	33 (67%)
Inflammation, suppurative				1 (2%)	1 (2%)
Inflammation, granulomatous		1 (2%)			
Inflammation, chronic	1 (2%)			1 (2%)	1 (2%)
Metaplasia, osseous		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis	1 (2%)	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia	11 (22%)	6 (12%)	4 (8%)	8 (16%)	5 (10%)
Alveolar epithelium, metaplasia, squamous			1 (2%)		
Nose	(50)	(50)	(49)	(50)	(49)
Foreign body	9 (18%)	11 (22%)	9 (18%)	15 (30%)	1 (2%)
Hemorrhage		1 (2%)			
Inflammation, chronic	8 (16%)	11 (22%)	8 (16%)	16 (32%)	7 (14%)
Thrombosis	1 (2%)				
Nasolacrimal duct, cyst				2 (4%)	1 (2%)
Respiratory epithelium, hyperplasia	5 (10%)	5 (10%)	4 (8%)	11 (22%)	4 (8%)
Respiratory epithelium, metaplasia, squamous		1 (2%)		3 (6%)	1 (2%)
Special Senses System					
Eye	(50)	(50)	(49)	(50)	(49)
Cataract	1 (2%)	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Hemorrhage					1 (2%)
Inflammation, chronic		1 (2%)			3 (6%)
Cornea, hyperplasia					1 (2%)
Retina, degeneration	2 (4%)	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Harderian gland	(50)	(50)	(49)	(50)	(49)
Inflammation, chronic	2 (4%)	1 (2%)			
Pigmentation					1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Urinary System					
Kidney	(50)	(50)	(49)	(50)	(49)
Cyst		2 (4%)	1 (2%)	4 (8%)	1 (2%)
Hydronephrosis					1 (2%)
Infarct				1 (2%)	
Infiltration cellular, lipocyte			1 (2%)		
Inflammation, chronic	5 (10%)	9 (18%)	8 (16%)	2 (4%)	2 (4%)
Nephropathy	45 (90%)	43 (86%)	45 (92%)	43 (86%)	41 (84%)
Renal tubule, accumulation, hyaline droplet			2 (4%)		
Renal tubule, dilatation			3 (6%)		1 (2%)
Renal tubule, hyperplasia				2 (4%)	
Renal tubule, necrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Renal tubule, pigmentation	5 (10%)	1 (2%)	1 (2%)		3 (6%)
Transitional epithelium, hyperplasia			1 (2%)		
Urinary bladder	(50)	(50)	(49)	(50)	(49)
Calculus microscopic observation only			1 (2%)		
Edema			1 (2%)		
Hemorrhage		1 (2%)	1 (2%)		
Inflammation, chronic			1 (2%)		
Necrosis		1 (2%)			
Transitional epithelium, hyperplasia		1 (2%)			1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM DICHROMATE DIHYDRATE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	12	15	9	10	18
Natural deaths	5	3	9	4	1
Survivors					
Died last week of study	1				
Terminal sacrifice	32	32	32	36	31
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, cecum	(46)	(47)	(48)	(47)	(50)
Intestine large, colon	(49)	(49)	(49)	(48)	(50)
Adenoma		1 (2%)			
Intestine small, duodenum	(46)	(49)	(48)	(46)	(50)
Leiomyoma	1 (2%)				
Intestine small, ileum	(45)	(47)	(44)	(47)	(50)
Intestine small, jejunum	(46)	(46)	(44)	(45)	(49)
Liver	(50)	(50)	(50)	(50)	(50)
Hepatocellular adenoma	1 (2%)	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)			
Sarcoma, metastatic, tissue NOS					1 (2%)
Mesentery	(11)	(13)	(12)	(15)	(10)
Sarcoma				1 (7%)	
Oral mucosa	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma				2 (4%)	11 (22%)
Pancreas	(50)	(50)	(50)	(50)	(50)
Mixed tumor benign			1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Tongue	(45)	(49)	(48)	(48)	(48)
Squamous cell carcinoma				1 (2%)	
Squamous cell carcinoma, metastatic, oral mucosa					2 (4%)
Squamous cell papilloma	1 (2%)	1 (2%)			
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Schwannoma malignant	1 (2%)	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)			
Adrenal medulla	(49)	(50)	(49)	(50)	(50)
Pheochromocytoma benign	2 (4%)	1 (2%)	2 (4%)	4 (8%)	
Pheochromocytoma benign, multiple		1 (2%)			
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Pheochromocytoma malignant, multiple		1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Adenoma, multiple				1 (2%)	
Parathyroid gland	(46)	(47)	(47)	(45)	(47)
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Pars distalis, adenoma	26 (52%)	29 (58%)	25 (50%)	21 (42%)	12 (24%)
Pars distalis, adenoma, multiple	2 (4%)			1 (2%)	
Pars distalis, carcinoma	2 (4%)	1 (2%)		1 (2%)	1 (2%)
Pars intermedia, adenoma					1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)	(50)
C-cell, adenoma	8 (16%)	5 (10%)	7 (14%)	4 (8%)	9 (18%)
C-cell, carcinoma	2 (4%)			2 (4%)	2 (4%)
Follicular cell, adenoma					1 (2%)
Follicular cell, carcinoma		1 (2%)	1 (2%)		1 (2%)
General Body System					
Tissue NOS					(2)
Abdominal, sarcoma					1 (50%)
Genital System					
Clitoral gland	(50)	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	9 (18%)	8 (16%)	5 (10%)	4 (8%)
Carcinoma	8 (16%)	8 (16%)	5 (10%)	3 (6%)	5 (10%)
Carcinoma, multiple		3 (6%)			
Fibrosarcoma		1 (2%)			
Bilateral, adenoma					1 (2%)
Ovary	(49)	(50)	(50)	(50)	(50)
Granulosa cell tumor benign		1 (2%)		1 (2%)	
Uterus	(49)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)				
Leiomyosarcoma			1 (2%)		
Polyp stromal	10 (20%)	14 (28%)	13 (26%)	15 (30%)	8 (16%)
Polyp stromal, multiple		1 (2%)	1 (2%)	2 (4%)	
Schwannoma malignant			1 (2%)	1 (2%)	1 (2%)
Schwannoma malignant, metastatic, uterus	1 (2%)				
Vagina	(8)	(12)	(4)	(4)	(10)
Polyp		1 (8%)			
Schwannoma malignant					1 (10%)
Schwannoma malignant, metastatic, vagina	1 (13%)				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)			
Lymph node	(8)	(11)	(9)	(4)	(11)
Lymph node, mandibular	(4)		(3)	(2)	(3)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Lymph node, pancreatic	(29)	(36)	(30)	(34)	(33)
Spleen	(50)	(50)	(50)	(50)	(50)
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)			
Thymus	(50)	(49)	(49)	(48)	(47)
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	3 (6%)		
Carcinoma		3 (6%)	1 (2%)	1 (2%)	
Fibroadenoma	13 (26%)	16 (32%)	20 (40%)	19 (38%)	14 (28%)
Fibroadenoma, multiple	24 (48%)	15 (30%)	17 (34%)	11 (22%)	9 (18%)
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)			
Keratoacanthoma	1 (2%)				
Sebaceous gland, adenoma	1 (2%)		1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)		4 (8%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibroma, multiple				1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)			
Subcutaneous tissue, lipoma		1 (2%)		1 (2%)	
Subcutaneous tissue, liposarcoma			1 (2%)		
Subcutaneous tissue, sarcoma				1 (2%)	
Subcutaneous tissue, schwannoma malignant		1 (2%)			
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)	1 (2%)		1 (2%)	1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa					1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Respiratory System					
Larynx				(1)	(1)
Squamous cell carcinoma					1 (100%)
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Carcinoma, metastatic, clitoral gland		1 (2%)			
Carcinoma, metastatic, uncertain primary site					1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa					2 (4%)
Nose	(50)	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, oral mucosa					1 (2%)
Special Senses System					
Eye	(50)	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(50)	(50)
Adenoma				1 (2%)	
Squamous cell carcinoma, metastatic, oral mucosa				1 (2%)	1 (2%)
Zymbal's gland	(1)				(1)
Carcinoma	1 (100%)				1 (100%)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Urinary bladder	(49)	(50)	(50)	(50)	(49)
Papilloma					1 (2%)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Leukemia mononuclear	8 (16%)	18 (36%)	13 (26%)	7 (14%)	11 (22%)
Neoplasm Summary					
Moribund	12	15	9	10	18
Total animals with primary neoplasms[c]	49	48	50	49	47
Total primary neoplasms	126	144	130	114	104
Total animals with benign neoplasms	47	46	47	46	37
Total benign neoplasms	103	103	106	93	68
Total animals with malignant neoplasms	19	30	19	18	30
Total malignant neoplasms	23	41	24	21	36
Total animals with metastatic neoplasms	2	3		2	8
Total metastatic neoplasms	3	5		2	10
Total animals with malignant neoplasms of uncertain primary site					1

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

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Adrenal Medulla: Benign Pheochromocytoma					
Overall rate[a]	2/49 (4%)	2/50 (4%)	2/49 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate[b]	4.6%	4.6%	4.6%	9.3%	0.0%
Terminal rate[c]	2/33 (6%)	2/32 (6%)	1/31 (3%)	4/36 (11%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	662	729 (T)	—[d]
Poly-3 test[e]	P=0.200N	P=0.692N	P=0.693	P=0.334	P=0.240N
Adrenal Medulla: Benign or Malignant Pheochromocytoma					
Overall rate	3/49 (6%)	4/50 (8%)	3/49 (6%)	5/50 (10%)	0/50 (0%)
Adjusted rate	6.9%	9.0%	6.8%	11.6%	0.0%
Terminal rate	3/33 (9%)	3/32 (9%)	1/31 (3%)	5/36 (14%)	0/31 (0%)
First incidence (days)	729 (T)	618	571	729 (T)	—
Poly-3 test	P=0.084N	P=0.509	P=0.658N	P=0.352	P=0.121N
Clitoral Gland: Adenoma					
Overall rate	2/50 (4%)	9/50 (18%)	8/50 (16%)	5/50 (10%)	5/50 (10%)
Adjusted rate	4.5%	20.5%	18.0%	11.6%	11.5%
Terminal rate	1/33 (3%)	8/32 (25%)	7/32 (22%)	5/36 (14%)	4/31 (13%)
First incidence (days)	689	689	689	729 (T)	605
Poly-3 test	P=0.437N	P=0.023	P=0.044	P=0.204	P=0.204
Clitoral Gland: Carcinoma					
Overall rate	8/50 (16%)	11/50 (22%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	17.9%	24.6%	11.3%	6.8%	11.7%
Terminal rate	6/33 (18%)	8/32 (25%)	5/32 (16%)	1/36 (3%)	5/31 (16%)
First incidence (days)	654	605	729 (T)	447	729 (T)
Poly-3 test	P=0.138N	P=0.302	P=0.283N	P=0.100N	P=0.302N
Clitoral Gland: Adenoma or Carcinoma					
Overall rate	10/50 (20%)	19/50 (38%)	13/50 (26%)	8/50 (16%)	10/50 (20%)
Adjusted rate	22.3%	42.3%	29.3%	18.0%	23.1%
Terminal rate	7/33 (21%)	15/32 (47%)	12/32 (38%)	6/36 (17%)	9/31 (29%)
First incidence (days)	654	605	689	447	605
Poly-3 test	P=0.156N	P=0.032	P=0.301	P=0.406N	P=0.564
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	4/50 (8%)	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	9.0%	6.8%	4.5%	6.9%	7.0%
Terminal rate	4/33 (12%)	3/32 (9%)	2/32 (6%)	3/36 (8%)	2/31 (7%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)	721
Poly-3 test	P=0.579N	P=0.507N	P=0.339N	P=0.514N	P=0.518N
Mammary Gland: Fibroadenoma					
Overall rate	37/50 (74%)	31/50 (62%)	37/50 (74%)	30/50 (60%)	23/50 (46%)
Adjusted rate	77.3%	67.4%	79.3%	66.4%	52.1%
Terminal rate	26/33 (79%)	23/32 (72%)	26/32 (81%)	25/36 (69%)	18/31 (58%)
First incidence (days)	489	560	571	559	560
Poly-3 test	P=0.003N	P=0.191N	P=0.505	P=0.165N	P=0.007N

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Mammary Gland: Adenoma					
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	4.5%	2.3%	6.7%	0.0%	0.0%
Terminal rate	2/33 (6%)	1/32 (3%)	2/32 (6%)	0/36 (0%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	586	—	—
Poly-3 test	P=0.119N	P=0.504N	P=0.503	P=0.243N	P=0.245N
Mammary Gland: Fibroadenoma or Adenoma					
Overall rate	37/50 (74%)	31/50 (62%)	38/50 (76%)	30/50 (60%)	23/50 (46%)
Adjusted rate	77.3%	67.4%	80.6%	66.4%	52.1%
Terminal rate	26/33 (79%)	23/32 (72%)	26/32 (81%)	25/36 (69%)	18/31 (58%)
First incidence (days)	489	560	571	559	560
Poly-3 test	P=0.002N	P=0.191N	P=0.439	P=0.165N	P=0.007N
Mammary Gland: Carcinoma					
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	6.8%	2.3%	2.3%	0.0%
Terminal rate	0/33 (0%)	2/32 (6%)	1/32 (3%)	1/36 (3%)	0/31 (0%)
First incidence (days)	—	686	729 (T)	729 (T)	—[f]
Poly-3 test	P=0.236N	P=0.117	P=0.499	P=0.495	—
Mammary Gland: Adenoma or Carcinoma					
Overall rate	2/50 (4%)	4/50 (8%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate	4.5%	9.1%	9.0%	2.3%	0.0%
Terminal rate	2/33 (6%)	3/32 (9%)	3/32 (9%)	1/36 (3%)	0/31 (0%)
First incidence (days)	729 (T)	686	586	729 (T)	—
Poly-3 test	P=0.050N	P=0.333	P=0.340	P=0.509N	P=0.245N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma					
Overall rate	37/50 (74%)	31/50 (62%)	39/50 (78%)	30/50 (60%)	23/50 (46%)
Adjusted rate	77.3%	67.4%	82.7%	66.4%	52.1%
Terminal rate	26/33 (79%)	23/32 (72%)	27/32 (84%)	25/36 (69%)	18/31 (58%)
First incidence (days)	489	560	571	559	560
Poly-3 test	P=0.002N	P=0.191N	P=0.335	P=0.165N	P=0.007N
Oral Cavity (Oral Mucosa): Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)[g]	11/50 (22%)
Adjusted rate	0.0%	0.0%	0.0%	4.6%	23.9%
Terminal rate	0/33 (0%)	0/32 (0%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First incidence (days)	—	—	—	646	506
Poly-3 test	P<0.001	—	—	P=0.233	P<0.001
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	11/50 (22%)
Adjusted rate	2.2%	2.3%	0.0%	4.6%	23.9%
Terminal rate	0/33 (0%)	1/32 (3%)	0/32 (0%)	1/36 (3%)	2/31 (7%)
First incidence (days)	618	729 (T)	—	646	506
Poly-3 test	P<0.001	P=0.756	P=0.503N	P=0.491	P=0.002

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Pancreatic Islets: Adenoma					
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.5%	2.3%	4.5%	6.9%	4.7%
Terminal rate	1/33 (3%)	1/32 (3%)	1/32 (3%)	3/36 (8%)	2/31 (7%)
First incidence (days)	721	729 (T)	586	729 (T)	729 (T)
Poly-3 test	P=0.491	P=0.504N	P=0.692N	P=0.488	P=0.682
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	28/50 (56%)	29/50 (58%)	25/50 (50%)	22/50 (44%)	12/49 (24%)
Adjusted rate	60.5%	61.3%	54.0%	48.3%	27.8%
Terminal rate	20/33 (61%)	18/32 (56%)	16/32 (50%)	16/36 (44%)	9/31 (29%)
First incidence (days)	489	461	534	580	647
Poly-3 test	P<0.001N	P=0.553	P=0.334N	P=0.164N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma					
Overall rate	30/50 (60%)	30/50 (60%)	25/50 (50%)	23/50 (46%)	13/49 (27%)
Adjusted rate	63.8%	63.4%	54.0%	50.5%	30.1%
Terminal rate	20/33 (61%)	19/32 (59%)	16/32 (50%)	17/36 (47%)	10/31 (32%)
First incidence (days)	489	461	534	580	647
Poly-3 test	P<0.001N	P=0.571N	P=0.221N	P=0.135N	P<0.001N
Skin (Subcutaneous Tissue): Fibroma					
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.3%	0.0%	9.1%	4.6%	6.9%
Terminal rate	1/33 (3%)	0/32 (0%)	4/32 (13%)	2/36 (6%)	2/31 (7%)
First incidence (days)	729 (T)	—	729 (T)	729 (T)	605
Poly-3 test	P=0.226	P=0.502N	P=0.177	P=0.491	P=0.296
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma					
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	2.3%	2.2%	9.1%	6.9%	6.9%
Terminal rate	1/33 (3%)	0/32 (0%)	4/32 (13%)	2/36 (6%)	2/31 (7%)
First incidence (days)	729 (T)	461	729 (T)	559	605
Poly-3 test	P=0.299	P=0.760N	P=0.177	P=0.300	P=0.296
Thyroid Gland (C-cell): Adenoma					
Overall rate	8/50 (16%)	5/50 (10%)	7/50 (14%)	4/50 (8%)	9/50 (18%)
Adjusted rate	17.8%	11.2%	15.8%	9.1%	20.8%
Terminal rate	6/33 (18%)	3/32 (9%)	7/32 (22%)	3/36 (8%)	8/31 (26%)
First incidence (days)	580	560	729 (T)	379	595
Poly-3 test	P=0.250	P=0.280N	P=0.515N	P=0.185N	P=0.466
Thyroid Gland (C-cell): Adenoma or Carcinoma					
Overall rate	10/50 (20%)	5/50 (10%)	7/50 (14%)	5/50 (10%)	10/50 (20%)
Adjusted rate	22.0%	11.2%	15.8%	11.3%	23.1%
Terminal rate	7/33 (21%)	3/32 (9%)	7/32 (22%)	4/36 (11%)	9/31 (29%)
First incidence (days)	580	560	729 (T)	379	595
Poly-3 test	P=0.232	P=0.135N	P=0.316N	P=0.140N	P=0.555

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Uterus: Stromal Polyp					
Overall rate	10/50 (20%)	15/50 (30%)	14/50 (28%)	17/50 (34%)	8/50 (16%)
Adjusted rate	22.5%	32.7%	31.0%	37.8%	18.1%
Terminal rate	10/33 (30%)	9/32 (28%)	10/32 (31%)	13/36 (36%)	5/31 (16%)
First incidence (days)	729 (T)	554	586	493	461
Poly-3 test	P=0.139N	P=0.198	P=0.251	P=0.087	P=0.399N
All Organs: Mononuclear Cell Leukemia					
Overall rate	8/50 (16%)	18/50 (36%)	13/50 (26%)	7/50 (14%)	11/50 (22%)
Adjusted rate	17.4%	38.4%	27.9%	15.3%	24.5%
Terminal rate	2/33 (6%)	8/32 (25%)	7/32 (22%)	2/36 (6%)	6/31 (19%)
First incidence (days)	575	387	554	379	472
Poly-3 test	P=0.348N	P=0.019	P=0.170	P=0.503N	P=0.282
All Organs: Benign Neoplasms					
Overall rate	47/50 (94%)	46/50 (92%)	47/50 (94%)	46/50 (92%)	37/50 (74%)
Adjusted rate	95.7%	94.6%	96.8%	94.9%	79.6%
Terminal rate	32/33 (97%)	31/32 (97%)	32/32 (100%)	35/36 (97%)	26/31 (84%)
First incidence (days)	489	461	534	379	461
Poly-3 test	P<0.001N	P=0.596N	P=0.620	P=0.628N	P=0.009N
All Organs: Malignant Neoplasms					
Overall rate	20/50 (40%)	30/50 (60%)	19/50 (38%)	18/50 (36%)	31/50 (62%)
Adjusted rate	42.1%	62.4%	39.4%	37.2%	63.1%
Terminal rate	10/33 (30%)	18/32 (56%)	10/32 (31%)	8/36 (22%)	15/31 (48%)
First incidence (days)	575	387	454	379	461
Poly-3 test	P=0.057	P=0.034	P=0.475N	P=0.389N	P=0.029
All Organs: Benign or Malignant Neoplasms					
Overall rate	49/50 (98%)	48/50 (96%)	50/50 (100%)	49/50 (98%)	47/50 (94%)
Adjusted rate	98.0%	96.6%	100.0%	98.0%	94.0%
Terminal rate	32/33 (97%)	31/32 (97%)	32/32 (100%)	35/36 (97%)	28/31 (90%)
First incidence (days)	489	387	454	379	461
Poly-3 test	P=0.126N	P=0.575N	P=0.500	P=0.760	P=0.306N

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

TABLE B3
Historical Incidence of Oral Cavity Neoplasms in Control Female F344/N Rats[a]

Study	Incidence in Controls	
	Oral Mucosa	All Sites[b]
	Squamous Cell Carcinoma	Papilloma, Squamous Cell Papilloma, or Squamous Cell Carcinoma
Historical Incidence: Drinking Water Studies		
Bromochloroacetic acid	0/50	1/50
Dibromoacetic acid	0/50	0/50
Dibromoacetonitrile	0/50	1/50
Dipropylene glycol	0/50	1/50
Sodium chlorate	0/50	0/50
Sodium dichromate dihydrate	0/50	—
Overall Historical Incidences: Drinking Water Studies		
Total (%)	0/300	3/250 (1.2%)
Mean ± standard deviation		1.2% ± 1.1%
Range		(0%-2%)
Overall Historical Incidence: All Routes		
Total (%)	5/1,400 (0.4%)	14/1,350 (1.0%)
Mean ± standard deviation	0.4% ± 0.8%	1.1% ± 1.6%
Range	(0%-2%)	(0%-6%)

[a] Data as of March 5, 2007, with sodium dichromate dihydrate data added from Table B1
[b] All sites includes the oral mucosa, tongue, pharynx, tooth, and gingiva; sodium dichromate dihydrate data not included

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	12	15	9	10	18
Natural deaths	5	3	9	4	1
Survivors					
Died last week of study	1				
Terminal sacrifice	32	32	32	36	31
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Intestine large, cecum	(46)	(47)	(48)	(47)	(50)
Edema	2 (4%)	1 (2%)	1 (2%)		1 (2%)
Hemorrhage			1 (2%)		
Intestine large, colon	(49)	(49)	(49)	(48)	(50)
Intestine small, duodenum	(46)	(49)	(48)	(46)	(50)
Infiltration cellular, histiocyte			1 (2%)	30 (65%)	47 (94%)
Intestine small, ileum	(45)	(47)	(44)	(47)	(50)
Lymphatic, hyperplasia				1 (2%)	
Lymphoid tissue, hyperplasia	16 (36%)	10 (21%)	8 (18%)	6 (13%)	12 (24%)
Intestine small, jejunum	(46)	(46)	(44)	(45)	(49)
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	4 (8%)	2 (4%)		
Basophilic focus	45 (90%)	41 (82%)	44 (88%)	47 (94%)	43 (86%)
Clear cell focus	7 (14%)	5 (10%)	7 (14%)	20 (40%)	7 (14%)
Eosinophilic focus	5 (10%)	5 (10%)	5 (10%)	3 (6%)	3 (6%)
Fatty change	3 (6%)	7 (14%)	10 (20%)	13 (26%)	16 (32%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		3 (6%)	
Hemorrhage		1 (2%)	1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	5 (10%)	3 (6%)	9 (18%)	10 (20%)	9 (18%)
Infiltration cellular, histiocyte	1 (2%)	5 (10%)	21 (42%)	42 (84%)	47 (94%)
Inflammation, chronic	12 (24%)	21 (42%)	28 (56%)	35 (70%)	39 (78%)
Mixed cell focus	9 (18%)	6 (12%)	10 (20%)	20 (40%)	18 (36%)
Necrosis	5 (10%)	7 (14%)	4 (8%)		1 (2%)
Regeneration		1 (2%)	1 (2%)		
Bile duct, hyperplasia	2 (4%)		5 (10%)	3 (6%)	4 (8%)
Centrilobular, necrosis	4 (8%)	2 (4%)	1 (2%)	2 (4%)	
Hepatocyte, syncytial alteration				1 (2%)	1 (2%)
Kupffer cell, pigmentation	1 (2%)	1 (2%)			
Lymphatic, infiltration cellular				1 (2%)	
Mesentery	(11)	(13)	(12)	(15)	(10)
Accessory spleen		1 (8%)		1 (7%)	1 (10%)
Fat, necrosis	11 (100%)	10 (77%)	11 (92%)	12 (80%)	9 (90%)
Oral mucosa	(50)	(50)	(50)	(50)	(50)
Pancreas	(50)	(50)	(50)	(50)	(50)
Atrophy	6 (12%)	12 (24%)	11 (22%)	9 (18%)	5 (10%)
Cyst	2 (4%)	4 (8%)	3 (6%)	6 (12%)	4 (8%)
Acinus, cytoplasmic alteration					3 (6%)
Acinus, hyperplasia, focal	1 (2%)		1 (2%)		1 (2%)

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Alimentary System (continued)					
Salivary glands	(50)	(50)	(50)	(50)	(50)
Atrophy	9 (18%)	7 (14%)	10 (20%)	17 (34%)	17 (34%)
Fibrosis		1 (2%)			
Vacuolization cytoplasmic		1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)	(50)
Edema	1 (2%)	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Erosion			1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active					1 (2%)
Ulcer	2 (4%)	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Epithelium, hyperplasia	2 (4%)	3 (6%)	4 (8%)	4 (8%)	4 (8%)
Stomach, glandular	(50)	(50)	(50)	(50)	(50)
Edema			1 (2%)	1 (2%)	1 (2%)
Erosion	2 (4%)	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Hyperplasia	4 (8%)	6 (12%)	4 (8%)	7 (14%)	4 (8%)
Inflammation					1 (2%)
Ulcer	1 (2%)	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Glands, dilatation			1 (2%)		
Tongue	(45)	(49)	(48)	(48)	(48)
Granuloma					2 (4%)
Hemorrhage		1 (2%)			1 (2%)
Inflammation, chronic	8 (18%)	3 (6%)	4 (8%)	14 (29%)	12 (25%)
Ulcer					3 (6%)
Epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)		
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	27 (54%)	32 (64%)	35 (70%)	33 (66%)	28 (56%)
Inflammation, chronic		1 (2%)			
Necrosis			1 (2%)		
Thrombosis	1 (2%)	1 (2%)	2 (4%)	1 (2%)	
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	6 (12%)	9 (18%)	10 (20%)	6 (12%)	8 (16%)
Angiectasis	1 (2%)	1 (2%)			
Degeneration, fatty	12 (24%)	12 (24%)	17 (34%)	14 (28%)	20 (40%)
Hyperplasia, focal	2 (4%)	6 (12%)	8 (16%)	12 (24%)	6 (12%)
Hypertrophy	1 (2%)				
Hypertrophy, focal	4 (8%)	4 (8%)	6 (12%)	1 (2%)	7 (14%)
Necrosis	3 (6%)			2 (4%)	
Adrenal medulla	(49)	(50)	(49)	(50)	(50)
Hyperplasia	2 (4%)	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)		
Parathyroid gland	(46)	(47)	(47)	(45)	(47)
Hyperplasia		1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Endocrine System (continued)					
Pituitary gland	(50)	(50)	(50)	(50)	(49)
Pars distalis, angiectasis	11 (22%)	6 (12%)	7 (14%)	4 (8%)	3 (6%)
Pars distalis, cyst	18 (36%)	18 (36%)	18 (36%)	18 (36%)	27 (55%)
Pars distalis, cytoplasmic alteration, focal				1 (2%)	
Pars distalis, hyperplasia					1 (2%)
Pars distalis, hyperplasia, focal	9 (18%)	8 (16%)	9 (18%)	8 (16%)	10 (20%)
Pars intermedia, angiectasis	1 (2%)	2 (4%)			
Pars intermedia, cyst	1 (2%)	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Ultimobranchial cyst			2 (4%)		2 (4%)
C-cell, hyperplasia	28 (56%)	28 (56%)	25 (50%)	23 (46%)	16 (32%)
Follicle, cyst		1 (2%)			
General Body System					
Tissue NOS					(2)
Genital System					
Clitoral gland	(50)	(50)	(50)	(50)	(50)
Cyst	2 (4%)		2 (4%)	4 (8%)	1 (2%)
Hyperplasia	4 (8%)	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Inflammation				1 (2%)	
Inflammation, chronic	3 (6%)	4 (8%)	6 (12%)	8 (16%)	4 (8%)
Ovary	(49)	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		1 (2%)	
Cyst	9 (18%)	6 (12%)	7 (14%)	10 (20%)	5 (10%)
Uterus	(49)	(50)	(50)	(50)	(50)
Angiectasis					2 (4%)
Dilatation		1 (2%)			
Hemorrhage		1 (2%)			
Hyperplasia, cystic	5 (10%)	5 (10%)	4 (8%)	9 (18%)	5 (10%)
Inflammation, chronic				1 (2%)	
Vagina	(8)	(12)	(4)	(4)	(10)
Angiectasis	1 (13%)				
Hematopoietic System					
Bone marrow	(50)	(50)	(49)	(50)	(50)
Hyperplasia	6 (12%)	8 (16%)	7 (14%)	6 (12%)	9 (18%)
Infiltration cellular, histiocyte	1 (2%)		2 (4%)		
Myelofibrosis		1 (2%)		1 (2%)	1 (2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematopoietic System (continued)					
Lymph node	(8)	(11)	(9)	(4)	(11)
Hemorrhage	1 (13%)			1 (25%)	
Hyperplasia, lymphoid				1 (25%)	
Deep cervical, hemorrhage	1 (13%)		1 (11%)		
Mediastinal, ectasia		1 (9%)			2 (6%)
Mediastinal, hemorrhage	3 (38%)	4 (36%)	2 (22%)	3 (75%)	4 (36%)
Mediastinal, hyperplasia, lymphoid	2 (25%)	5 (45%)	2 (22%)	1 (25%)	6 (55%)
Mediastinal, pigmentation	1 (13%)	4 (36%)		2 (50%)	1 (9%)
Lymph node, mandibular	(4)		(3)	(2)	(3)
Ectasia					1 (33%)
Lymph node, mesenteric	(50)	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)		
Hemorrhage	11 (22%)	13 (26%)	16 (32%)	14 (28%)	21 (42%)
Hyperplasia, lymphoid			2 (4%)		
Hyperplasia, reticulum cell			1 (2%)		1 (2%)
Infiltration cellular, histiocyte	21 (42%)	18 (36%)	27 (54%)	36 (72%)	42 (84%)
Lymph node, pancreatic	(29)	(36)	(30)	(34)	(33)
Hemorrhage	3 (10%)		2 (7%)		4 (12%)
Hyperplasia, lymphoid					2 (6%)
Infiltration cellular, histiocyte	17 (59%)	20 (56%)	23 (77%)	32 (94%)	27 (82%)
Pigmentation	2 (7%)				1 (3%)
Spleen	(50)	(50)	(50)	(50)	(50)
Accessory spleen			1 (2%)		1 (2%)
Fibrosis		2 (4%)			
Hematopoietic cell proliferation	36 (72%)	28 (56%)	38 (76%)	36 (72%)	33 (66%)
Hemorrhage			1 (2%)		1 (2%)
Infiltration cellular, mixed cell			3 (6%)		
Necrosis		3 (6%)	1 (2%)	1 (2%)	2 (4%)
Pigmentation	26 (52%)	23 (46%)	13 (26%)	6 (12%)	3 (6%)
Lymphoid follicle, atrophy				1 (2%)	4 (8%)
Lymphoid follicle, hyperplasia			1 (2%)		3 (6%)
Thymus	(50)	(49)	(49)	(48)	(47)
Atrophy					3 (6%)
Integumentary System					
Mammary gland	(50)	(50)	(50)	(50)	(50)
Hyperplasia	47 (94%)	50 (100%)	45 (90%)	49 (98%)	44 (88%)
Skin	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			1 (2%)	
Edema		1 (2%)			
Hyperkeratosis			1 (2%)		
Ulcer			1 (2%)		
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Cranium, osteopetrosis			1 (2%)	1 (2%)	2 (4%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Compression	8 (16%)	13 (26%)	15 (30%)	11 (22%)	7 (14%)
Gliosis					1 (2%)
Hemorrhage	1 (2%)	3 (6%)		1 (2%)	
Hydrocephalus			2 (4%)	2 (4%)	
Necrosis					1 (2%)
Vacuolization cytoplasmic					1 (2%)
Respiratory System					
Larynx				(1)	(1)
Lung	(50)	(50)	(50)	(50)	(50)
Edema			1 (2%)		
Foreign body			1 (2%)		1 (2%)
Hemorrhage	2 (4%)	4 (8%)	4 (8%)	1 (2%)	2 (4%)
Infiltration cellular, histiocyte	45 (90%)	48 (96%)	42 (84%)	46 (92%)	47 (94%)
Inflammation, chronic	2 (4%)	1 (2%)	3 (6%)		1 (2%)
Alveolar epithelium, hyperplasia	11 (22%)	7 (14%)	12 (24%)	9 (18%)	10 (20%)
Alveolar epithelium, metaplasia, squamous					1 (2%)
Nose	(50)	(50)	(50)	(50)	(50)
Foreign body	3 (6%)	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic	3 (6%)	2 (4%)		3 (6%)	3 (6%)
Nasolacrimal duct, cyst		1 (2%)			
Respiratory epithelium, hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Special Senses System					
Eye	(50)	(50)	(50)	(50)	(50)
Cataract	2 (4%)	2 (4%)	4 (8%)	1 (2%)	1 (2%)
Inflammation, chronic					3 (6%)
Retina, degeneration	4 (8%)	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Harderian gland	(50)	(50)	(50)	(50)	(50)
Hemorrhage					1 (2%)
Inflammation, chronic				1 (2%)	
Zymbal's gland	(1)				(1)
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(50)
Cyst				1 (2%)	2 (4%)
Glomerulosclerosis				1 (2%)	
Hydronephrosis				1 (2%)	
Infarct	3 (6%)	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)		1 (2%)
Nephropathy	33 (66%)	23 (46%)	32 (64%)	37 (74%)	41 (82%)
Renal tubule, accumulation, hyaline droplet	7 (14%)	4 (8%)	2 (4%)	2 (4%)	
Renal tubule, dilatation				1 (2%)	
Renal tubule, necrosis	3 (6%)	2 (4%)			
Renal tubule, pigmentation	2 (4%)	1 (2%)	1 (2%)		2 (4%)
Transitional epithelium, hyperplasia	3 (6%)	2 (4%)	2 (4%)		1 (2%)
Urinary bladder	(49)	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM DICHROMATE DIHYDRATE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	7	5	5	4	3
Natural deaths	10	10	10	8	15
Survivors					
Died last week of study	1				1
Terminal sacrifice	32	35	35	38	31
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(50)	(50)
Squamous cell papilloma					1 (2%)
Gallbladder	(47)	(45)	(44)	(44)	(39)
Sarcoma, metastatic, uncertain primary site				1 (2%)	
Intestine large, cecum	(42)	(44)	(47)	(46)	(39)
Carcinoma	1 (2%)		1 (2%)		
Intestine large, colon	(44)	(45)	(47)	(46)	(40)
Carcinoma					1 (3%)
Intestine large, rectum	(42)	(47)	(47)	(46)	(42)
Intestine small, duodenum	(39)	(43)	(45)	(48)	(40)
Adenoma	1 (3%)		1 (2%)	5 (10%)	9 (23%)
Adenoma, multiple					6 (15%)
Carcinoma				2 (4%)	3 (8%)
Hemangiosarcoma, metastatic, liver					1 (3%)
Hepatoblastoma, metastatic, liver	1 (3%)				
Sarcoma, metastatic, mesentery				1 (2%)	
Intestine small, ileum	(40)	(42)	(44)	(45)	(38)
Adenoma		1 (2%)			
Carcinoma			1 (2%)		
Intestine small, jejunum	(41)	(42)	(42)	(46)	(38)
Adenoma					3 (8%)
Carcinoma		1 (2%)		1 (2%)	2 (5%)
Carcinoma, multiple		1 (2%)			
Sarcoma, metastatic, mesentery				1 (2%)	
Liver	(50)	(50)	(50)	(50)	(50)
Hemangioma				1 (2%)	
Hemangiosarcoma	1 (2%)	1 (2%)	5 (10%)	2 (4%)	3 (6%)
Hemangiosarcoma, multiple					1 (2%)
Hepatoblastoma	14 (28%)	7 (14%)	10 (20%)	2 (4%)	
Hepatoblastoma, multiple	3 (6%)	1 (2%)	1 (2%)		
Hepatocellular adenoma	11 (22%)	12 (24%)	10 (20%)	12 (24%)	18 (36%)
Hepatocellular adenoma, multiple	25 (50%)	21 (42%)	18 (36%)	19 (38%)	10 (20%)
Hepatocellular carcinoma	10 (20%)	14 (28%)	8 (16%)	12 (24%)	14 (28%)
Hepatocellular carcinoma, multiple	4 (8%)	10 (20%)	9 (18%)		4 (8%)
Hepatocholangiocarcinoma					1 (2%)
Ito cell tumor malignant				2 (4%)	1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Alimentary System (continued)					
Mesentery	(16)	(10)	(9)	(16)	(5)
Carcinoma, metastatic, intestine large, cecum	1 (6%)				
Fibrosarcoma				1 (6%)	
Fibrosarcoma, metastatic, lung	1 (6%)				
Hemangiosarcoma				2 (13%)	
Hepatoblastoma, metastatic, liver	2 (13%)	2 (20%)			
Sarcoma				1 (6%)	
Sarcoma, metastatic, uncertain primary site				1 (6%)	
Oral mucosa	(50)	(50)	(50)	(50)	(50)
Pancreas	(49)	(49)	(50)	(49)	(48)
Fibrosarcoma, metastatic, lung	1 (2%)				
Hepatoblastoma, metastatic, liver	2 (4%)	1 (2%)			
Sarcoma, metastatic, mesentery				1 (2%)	
Salivary glands	(49)	(50)	(49)	(50)	(50)
Basal cell carcinoma, metastatic, skin	1 (2%)				
Stomach, forestomach	(50)	(50)	(48)	(50)	(48)
Carcinoma, metastatic, intestine large, cecum	1 (2%)				
Sarcoma, metastatic, uncertain primary site				1 (2%)	
Squamous cell carcinoma				1 (2%)	
Squamous cell papilloma				2 (4%)	
Stomach, glandular	(50)	(48)	(48)	(50)	(47)
Hepatoblastoma, metastatic, liver	1 (2%)				
Sarcoma, metastatic, mesentery				1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)	
Tongue	(50)	(50)	(50)	(50)	(50)
Tooth	(1)	(3)		(2)	
Cardiovascular System					
Blood vessel	(2)	(1)	(1)	(1)	(1)
Aorta, fibrosarcoma, metastatic, lung	1 (50%)				
Heart	(50)	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, lung	1 (2%)				
Hemangiosarcoma			1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone	1 (2%)				
Sarcoma, metastatic, uncertain primary site				1 (2%)	
Endocrine System					
Adrenal cortex	(49)	(49)	(50)	(50)	(50)
Adenoma			1 (2%)		1 (2%)
Hepatoblastoma, metastatic, liver	2 (4%)				
Hepatocellular carcinoma, metastatic, liver					1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)	
Capsule, adenoma	7 (14%)	5 (10%)	4 (8%)	6 (12%)	1 (2%)
Adrenal medulla	(49)	(48)	(50)	(50)	(50)
Pheochromocytoma benign				1 (2%)	1 (2%)
Islets, pancreatic	(49)	(49)	(50)	(50)	(49)
Adenoma	3 (6%)	1 (2%)	1 (2%)		
Parathyroid gland	(46)	(47)	(45)	(49)	(47)
Pituitary gland	(49)	(49)	(48)	(50)	(47)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Endocrine System (continued)					
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Basal cell carcinoma, metastatic, skin	1 (2%)				
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Follicular cell, carcinoma		1 (2%)	1 (2%)		
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver		1 (2%)			
Sarcoma, metastatic, mesentery				1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)	(50)
Prostate	(50)	(49)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver	1 (2%)				
Sarcoma, metastatic, mesentery				1 (2%)	
Testes	(50)	(50)	(50)	(50)	(50)
Hematopoietic System					
Bone marrow	(49)	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)		1 (2%)
Lymph node	(8)	(4)	(6)	(6)	(5)
Bronchial, hepatoblastoma, metastatic, liver			1 (17%)		
Bronchial, hepatocellular carcinoma, metastatic, liver			1 (17%)		
Bronchial, hepatocholangiocarcinoma, metastatic, liver					1 (20%)
Iliac, hemangiosarcoma, metastatic, skin				1 (17%)	
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (17%)		
Mediastinal, hepatocholangiocarcinoma, metastatic, liver					1 (20%)
Mediastinal, sarcoma, metastatic, uncertain primary site				1 (17%)	
Renal, hepatoblastoma, metastatic, liver	1 (17%)				
Lymph node, mandibular	(47)	(49)	(49)	(48)	(46)
Hemangiosarcoma					1 (2%)
Hemangiosarcoma, metastatic, spleen				1 (2%)	
Lymph node, mesenteric	(47)	(47)	(49)	(49)	(46)
Carcinoma, metastatic, intestine large, colon			1 (2%)		
Hemangioma				1 (2%)	
Hemangiosarcoma				1 (2%)	
Hepatoblastoma, metastatic, liver	1 (2%)				
Sarcoma, metastatic, mesentery				1 (2%)	
Lymph node, pancreatic	(5)	(13)	(10)	(8)	(16)
Hepatoblastoma, metastatic, liver			1 (10%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Hematopoietic System (continued)					
Spleen	(49)	(48)	(49)	(49)	(46)
Hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Thymus	(49)	(50)	(46)	(49)	(40)
Hepatoblastoma, metastatic, liver	1 (2%)				
Osteosarcoma, metastatic, bone	1 (2%)				
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Basal cell carcinoma	1 (2%)				
Hemangioma		1 (2%)			
Subcutaneous tissue, fibrosarcoma			1 (2%)		
Subcutaneous tissue, hemangiosarcoma			1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)				
Skeletal muscle	(4)	(2)	(4)	(1)	
Hepatoblastoma, metastatic, liver		1 (50%)			
Hepatocellular carcinoma, metastatic, liver			1 (25%)		
Osteosarcoma, metastatic, bone	1 (25%)				
Sarcoma, metastatic, mesentery				1 (100%)	
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)				
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	13 (26%)	8 (16%)	8 (16%)	6 (12%)	9 (18%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)	10 (20%)	6 (12%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		1 (2%)		
Basal cell carcinoma, metastatic, skin	1 (2%)				
Carcinoma, metastatic, Harderian gland		1 (2%)			
Carcinoma, metastatic, thyroid gland			1 (2%)		
Fibrosarcoma	1 (2%)				
Hemangiosarcoma			1 (2%)		
Hepatoblastoma, metastatic, liver	7 (14%)	3 (6%)	2 (4%)		
Hepatocellular carcinoma, metastatic, liver	4 (8%)	7 (14%)	2 (4%)	4 (8%)	7 (14%)
Hepatocholangiocarcinoma, metastatic, liver					1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)	
Sarcoma, metastatic, uncertain primary site				1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)			
Mediastinum, osteosarcoma, metastatic, bone	1 (2%)				
Nose	(50)	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Special Senses System					
Eye	(48)	(49)	(49)	(50)	(47)
Harderian gland	(50)	(50)	(49)	(50)	(50)
Adenoma	6 (12%)	3 (6%)	4 (8%)	3 (6%)	2 (4%)
Basal cell carcinoma, metastatic, skin	1 (2%)				
Carcinoma		1 (2%)			
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(49)
Sarcoma, metastatic, mesentery				1 (2%)	
Renal tubule, adenoma				1 (2%)	
Renal tubule, carcinoma		1 (2%)	1 (2%)		
Urethra	(1)	(1)		(1)	
Urinary bladder	(49)	(50)	(50)	(49)	(46)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)			1 (2%)
Lymphoma malignant	2 (4%)				2 (4%)
Mesothelioma malignant	2 (4%)				
Neoplasm Summary					
Total animals with primary neoplasms[c]	49	45	47	44	48
Total primary neoplasms	115	99	104	96	107
Total animals with benign neoplasms	42	37	33	42	37
Total benign neoplasms	69	54	49	60	63
Total animals with malignant neoplasms	31	29	36	27	29
Total malignant neoplasms	46	45	55	36	44
Total animals with metastatic neoplasms	15	11	9	8	10
Total metastatic neoplasms	38	17	11	26	13
Total animals with malignant neoplasms of uncertain primary site				1	

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

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Adrenal Cortex: Adenoma					
Overall rate[a]	7/49 (14%)	5/49 (10%)	5/50 (10%)	6/50 (12%)	2/50 (4%)
Adjusted rate[b]	15.6%	11.4%	11.4%	13.0%	4.6%
Terminal rate[c]	7/33 (21%)	5/35 (14%)	3/35 (9%)	6/38 (16%)	2/32 (6%)
First incidence (days)	729 (T)	729 (T)	664	729 (T)	729 (T)
Poly-3 test[d]	P=0.091N	P=0.398N	P=0.395N	P=0.476N	P=0.083N
Harderian Gland: Adenoma					
Overall rate	6/50 (12%)	3/50 (6%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	13.3%	6.8%	9.1%	6.4%	4.6%
Terminal rate	6/33 (18%)	3/35 (9%)	3/35 (9%)	2/38 (5%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	623	567	719
Poly-3 test	P=0.168N	P=0.251N	P=0.388N	P=0.224N	P=0.141N
Harderian Gland: Adenoma or Carcinoma					
Overall rate	6/50 (12%)	4/50 (8%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted rate	13.3%	9.0%	9.1%	6.4%	4.6%
Terminal rate	6/33 (18%)	4/35 (11%)	3/35 (9%)	2/38 (5%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	623	567	719
Poly-3 test	P=0.137N	P=0.382N	P=0.388N	P=0.224N	P=0.141N
Small Intestine (Duodenum): Adenoma					
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	5/50 (10%)	15/50 (30%)
Adjusted rate	2.2%	0.0%	2.3%	10.8%	32.9%
Terminal rate	0/33 (0%)	0/35 (0%)	1/35 (3%)	5/38 (13%)	10/32 (31%)
First incidence (days)	665	—[e]	729 (T)	729 (T)	451
Poly-3 test	P<0.001	P=0.505N	P=0.751	P=0.106	P<0.001
Small Intestine (Duodenum): Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	4.3%	6.8%
Terminal rate	0/33 (0%)	0/35 (0%)	0/35 (0%)	2/38 (5%)	3/32 (9%)
First incidence (days)	—	—[f]	—	729 (T)	729 (T)
Poly-3 test	P=0.011	—	—	P=0.243	P=0.113
Small Intestine (Jejunum): Adenoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	0.0%	6.8%
Terminal rate	0/33 (0%)	0/35 (0%)	0/35 (0%)	0/38 (0%)	2/32 (6%)
First incidence (days)	—	—	—	—	714
Poly-3 test	P=0.002	—	—	—	P=0.114
Small Intestine (Duodenum, Jejunum, or Ileum): Adenoma					
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)	17/50 (34%)
Adjusted rate	2.2%	2.3%	2.3%	10.8%	37.2%
Terminal rate	0/33 (0%)	1/35 (3%)	1/35 (3%)	5/38 (13%)	11/32 (34%)
First incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 test	P<0.001	P=0.755	P=0.751	P=0.106	P<0.001

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Small Intestine (Duodenum, Jejunum, or Ileum): Carcinoma					
Overall rate	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted rate	0.0%	4.5%	2.3%	6.5%	11.4%
Terminal rate	0/33 (0%)	2/35 (6%)	1/35 (3%)	3/38 (8%)	5/32 (16%)
First incidence (days)	—	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.014	P=0.233	P=0.492	P=0.123	P=0.028
Small Intestine (Duodenum, Jejunum, or Ileum): Adenoma or Carcinoma					
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	7/50 (14%)	20/50 (40%)
Adjusted rate	2.2%	6.8%	4.6%	15.1%	43.8%
Terminal rate	0/33 (0%)	3/35 (9%)	2/35 (6%)	7/38 (18%)	14/32 (44%)
First incidence (days)	665	729 (T)	729 (T)	729 (T)	451
Poly-3 test	P<0.001	P=0.296	P=0.485	P=0.032	P<0.001
Liver: Hemangiosarcoma					
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.2%	2.3%	11.4%	4.3%	9.1%
Terminal rate	1/33 (3%)	1/35 (3%)	4/35 (11%)	2/38 (5%)	2/32 (6%)
First incidence (days)	729 (T)	729 (T)	621	729 (T)	701
Poly-3 test	P=0.202	P=0.756	P=0.094	P=0.509	P=0.171
Liver: Hepatocellular Adenoma					
Overall rate	36/50 (72%)	33/50 (66%)	28/50 (56%)	31/50 (62%)	28/50 (56%)
Adjusted rate	77.2%	71.3%	62.5%	65.7%	60.8%
Terminal rate	29/33 (88%)	28/35 (80%)	24/35 (69%)	28/38 (74%)	22/32 (69%)
First incidence (days)	483	533	482	616	391
Poly-3 test	P=0.098N	P=0.333N	P=0.085N	P=0.147N	P=0.059N
Liver: Hepatocellular Carcinoma					
Overall rate	14/50 (28%)	24/50 (48%)	17/50 (34%)	12/50 (24%)	18/50 (36%)
Adjusted rate	29.3%	50.2%	36.8%	25.0%	38.0%
Terminal rate	5/33 (15%)	15/35 (43%)	11/35 (31%)	7/38 (18%)	8/32 (25%)
First incidence (days)	435	349	482	567	451
Poly-3 test	P=0.504N	P=0.028	P=0.291	P=0.405N	P=0.251
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	42/50 (84%)	42/50 (84%)	33/50 (66%)	37/50 (74%)	41/50 (82%)
Adjusted rate	86.3%	85.5%	71.2%	76.7%	82.9%
Terminal rate	30/33 (91%)	30/35 (86%)	26/35 (74%)	31/38 (82%)	26/32 (81%)
First incidence (days)	435	349	482	567	391
Poly-3 test	P=0.544	P=0.570N	P=0.050N	P=0.159N	P=0.422N
Liver: Hepatoblastoma					
Overall rate	17/50 (34%)	8/50 (16%)	11/50 (22%)	2/50 (4%)	0/50 (0%)
Adjusted rate	35.8%	17.7%	24.0%	4.3%	0.0%
Terminal rate	9/33 (27%)	6/35 (17%)	6/35 (17%)	2/38 (5%)	0/32 (0%)
First incidence (days)	435	587	544	729 (T)	—
Poly-3 test	P<0.001N	P=0.039N	P=0.153N	P<0.001N	P<0.001N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Liver: Hepatocellular Carcinoma or Hepatoblastoma					
Overall rate	25/50 (50%)	26/50 (52%)	26/50 (52%)	14/50 (28%)	18/50 (36%)
Adjusted rate	51.3%	53.9%	54.0%	29.2%	38.0%
Terminal rate	12/33 (36%)	16/35 (46%)	16/35 (46%)	9/38 (24%)	8/32 (25%)
First incidence (days)	435	349	482	567	451
Poly-3 test	P=0.035N	P=0.482	P=0.477	P=0.020N	P=0.132N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma					
Overall rate	46/50 (92%)	42/50 (84%)	37/50 (74%)	37/50 (74%)	41/50 (82%)
Adjusted rate	92.7%	85.5%	76.5%	76.7%	82.9%
Terminal rate	30/33 (91%)	30/35 (86%)	26/35 (74%)	31/38 (82%)	26/32 (81%)
First incidence (days)	435	349	482	567	391
Poly-3 test	P=0.323N	P=0.198N	P=0.023N	P=0.022N	P=0.114N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	15/50 (30%)	9/50 (18%)	9/50 (18%)	8/50 (16%)	11/50 (22%)
Adjusted rate	32.6%	20.1%	20.5%	17.2%	24.9%
Terminal rate	11/33 (33%)	8/35 (23%)	7/35 (20%)	7/38 (18%)	9/32 (28%)
First incidence (days)	631	533	604	693	632
Poly-3 test	P=0.495N	P=0.130N	P=0.144N	P=0.069N	P=0.282N
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	3/50 (6%)	5/50 (10%)	11/50 (22%)	6/50 (12%)	5/50 (10%)
Adjusted rate	6.6%	11.2%	25.0%	13.0%	11.3%
Terminal rate	2/33 (6%)	3/35 (9%)	8/35 (23%)	6/38 (16%)	4/32 (13%)
First incidence (days)	631	646	587	729 (T)	600
Poly-3 test	P=0.481N	P=0.348	P=0.015	P=0.250	P=0.342
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	16/50 (32%)	12/50 (24%)	16/50 (32%)	13/50 (26%)	16/50 (32%)
Adjusted rate	34.7%	26.4%	36.0%	28.0%	35.8%
Terminal rate	12/33 (36%)	9/35 (26%)	12/35 (34%)	12/38 (32%)	13/32 (41%)
First incidence (days)	631	533	587	693	600
Poly-3 test	P=0.394	P=0.262N	P=0.536	P=0.317N	P=0.546
Pancreatic Islets: Adenoma					
Overall rate	3/49 (6%)	1/49 (2%)	1/50 (2%)	0/50 (0%)	0/49 (0%)
Adjusted rate	6.6%	2.3%	2.3%	0.0%	0.0%
Terminal rate	2/33 (6%)	0/35 (0%)	0/35 (0%)	0/38 (0%)	0/32 (0%)
First incidence (days)	435	588	482	—	—
Poly-3 test	P=0.107N	P=0.319N	P=0.317N	P=0.116N	P=0.128N
All Organs: Hemangiosarcoma					
Overall rate	4/50 (8%)	1/50 (2%)	6/50 (12%)	6/50 (12%)	6/50 (12%)
Adjusted rate	8.9%	2.3%	13.7%	12.8%	13.6%
Terminal rate	4/33 (12%)	1/35 (3%)	5/35 (14%)	4/38 (11%)	4/32 (13%)
First incidence (days)	729 (T)	729 (T)	621	645	701
Poly-3 test	P=0.181	P=0.185N	P=0.350	P=0.392	P=0.354

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	4/50 (8%)	2/50 (4%)	6/50 (12%)	8/50 (16%)	6/50 (12%)
Adjusted rate	8.9%	4.5%	13.7%	17.0%	13.6%
Terminal rate	4/33 (12%)	2/35 (6%)	5/35 (14%)	5/38 (13%)	4/32 (13%)
First incidence (days)	729 (T)	729 (T)	621	645	701
Poly-3 test	P=0.222	P=0.346N	P=0.350	P=0.197	P=0.354
All Organs: Benign Neoplasms					
Overall rate	42/50 (84%)	37/50 (74%)	33/50 (66%)	42/50 (84%)	37/50 (74%)
Adjusted rate	86.9%	79.1%	72.7%	86.3%	77.0%
Terminal rate	31/33 (94%)	31/35 (89%)	27/35 (77%)	35/38 (92%)	25/32 (78%)
First incidence (days)	435	533	482	545	391
Poly-3 test	P=0.334N	P=0.214N	P=0.058N	P=0.587N	P=0.146N
All Organs: Malignant Neoplasms					
Overall rate	31/50 (62%)	29/50 (58%)	36/50 (72%)	28/50 (56%)	29/50 (58%)
Adjusted rate	63.2%	60.1%	74.1%	57.2%	61.0%
Terminal rate	17/33 (52%)	19/35 (54%)	24/35 (69%)	20/38 (53%)	17/32 (53%)
First incidence (days)	435	349	482	545	451
Poly-3 test	P=0.337N	P=0.457N	P=0.172	P=0.344N	P=0.493N
All Organs: Benign or Malignant Neoplasms					
Overall rate	49/50 (98%)	45/50 (90%)	47/50 (94%)	45/50 (90%)	48/50 (96%)
Adjusted rate	98.0%	91.6%	95.9%	91.5%	96.0%
Terminal rate	32/33 (97%)	33/35 (94%)	33/35 (94%)	36/38 (95%)	30/32 (94%)
First incidence (days)	435	349	482	545	391
Poly-3 test	P=0.552	P=0.146N	P=0.493N	P=0.145N	P=0.500N

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

TABLE C3
Historical Incidence of Small Intestine Neoplasms in Control Male B6C3F1 Mice[a]

Study	Incidence in Controls						
	Duodenum		Jejunum		Duodenum, Jejunum, or Ileum		
	Adenoma	Carcinoma	Adenoma	Carcinoma	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Drinking Water Studies							
Bromochloroacetic acid	3/50	1/50	0/50	1/50	3/50	2/50	5/50
Dibromoacetic acid	0/49	0/49	0/49	0/49	0/49	0/49	0/49
Dibromoacetonitrile	1/50	0/50	0/50	1/50	1/50	1/50	1/50
Dipropylene glycol	0/50	0/50	0/50	1/50	0/50	1/50	1/50
Sodium chlorate	1/50	0/50	0/50	2/50	1/50	2/50	3/50
Sodium dichromate dihydrate	1/50	0/50	0/50	0/50	1/50	0/50	1/50
Overall Historical Incidence: Drinking Water Studies							
Total (%)	6/299 (2.0%)	1/299 (0.3%)	0/299	5/299 (1.7%)	6/299 (2.0%)	6/299 (2.0%)	11/299 (3.7%)
Mean ± standard deviation	2.0% ± 2.2%	0.3% ± 0.8%		1.7% ± 1.5%	2.0% ± 2.2%	2.0% ± 1.8%	3.7% ± 3.7%
Range	(0%-6%)	(0%-2%)		(0%-4%)	(0%-6%)	(0%-4%)	(0%-10%)
Overall Historical Incidence: All Routes							
Total (%)	9/1,549 (0.6%)	3/1,549 (0.2%)	1/1,549 (0.1%)	25/1,549 (1.6%)	10/1,549 (0.6%)	30/1,549 (1.9%)	39/1,549 (2.5%)
Mean ± standard deviation	0.6% ± 1.3%	0.2% ± 0.8%	0.1% ± 0.4%	1.6% ± 2.2%	0.7% ± 1.3%	2.0% ± 2.2%	2.6% ± 2.7%
Range	(0%-6%)	(0%-4%)	(0%-2%)	(0%-8%)	(0%-6%)	(0%-8%)	(0%-10%)

[a] Data as of March 2, 2007, with sodium dichromate dihydrate data added from Table C1

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	7	5	5	4	3
Natural deaths	10	10	10	8	15
Survivors					
Died last week of study	1				1
Terminal sacrifice	32	35	35	38	31
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Esophagus	(50)	(50)	(50)	(50)	(50)
Gallbladder	(47)	(45)	(44)	(44)	(39)
Intestine large, cecum	(42)	(44)	(47)	(46)	(39)
Angiectasis	1 (2%)				
Fibrosis			1 (2%)		
Lymphoid tissue, hyperplasia			2 (4%)		
Intestine large, colon	(44)	(45)	(47)	(46)	(40)
Fibrosis			1 (2%)		
Lymphangiectasis	1 (2%)				
Lymphoid tissue, hyperplasia	1 (2%)		2 (4%)		2 (5%)
Intestine large, rectum	(42)	(47)	(47)	(46)	(42)
Inflammation, suppurative		1 (2%)			
Intestine small, duodenum	(39)	(43)	(45)	(48)	(40)
Erosion				1 (2%)	
Infiltration cellular, histiocyte		2 (5%)	4 (9%)	37 (77%)	35 (88%)
Infiltration cellular, mixed cell		1 (2%)			
Epithelium, hyperplasia, focal				1 (2%)	2 (5%)
Epithelium, hyperplasia, diffuse		11 (26%)	18 (40%)	42 (88%)	32 (80%)
Intestine small, ileum	(40)	(42)	(44)	(45)	(38)
Cyst			1 (2%)		
Infiltration cellular, polymorphonuclear			1 (2%)		
Inflammation, chronic active		1 (2%)			
Epithelium, hyperplasia, diffuse				1 (2%)	
Epithelium, inflammation, acute				1 (2%)	
Goblet cell, hyperplasia			1 (2%)		
Lymphoid tissue, hyperplasia			1 (2%)	2 (4%)	1 (3%)
Intestine small, jejunum	(41)	(42)	(42)	(46)	(38)
Fibrosis			1 (2%)		
Infiltration cellular, histiocyte				1 (2%)	
Inflammation, suppurative		1 (2%)			
Inflammation, chronic active			1 (2%)		
Epithelium, hyperplasia, focal		1 (2%)			
Epithelium, hyperplasia, diffuse				2 (4%)	1 (3%)
Lymphoid tissue, hyperplasia	2 (5%)	7 (17%)	5 (12%)	8 (17%)	3 (8%)
Liver	(50)	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)				
Basophilic focus	3 (6%)		4 (8%)		1 (2%)
Basophilic focus, multiple	1 (2%)				1 (2%)
Clear cell focus	8 (16%)	9 (18%)	13 (26%)	11 (22%)	6 (12%)
Clear cell focus, multiple	12 (24%)	8 (16%)	6 (12%)	5 (10%)	1 (2%)

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Alimentary System (continued)					
Liver (continued)	(50)	(50)	(50)	(50)	(50)
Congestion			1 (2%)		
Cyst			1 (2%)	1 (2%)	2 (4%)
Eosinophilic focus	17 (34%)	16 (32%)	13 (26%)	16 (32%)	10 (20%)
Eosinophilic focus, multiple	10 (20%)	10 (20%)	6 (12%)	5 (10%)	2 (4%)
Fibrosis				2 (4%)	
Hematopoietic cell proliferation		1 (2%)			
Hemorrhage		1 (2%)	1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	1 (2%)		2 (4%)		1 (2%)
Infarct					1 (2%)
Infiltration cellular, histiocyte	1 (2%)	3 (6%)	4 (8%)	4 (8%)	3 (6%)
Infiltration cellular, lymphocyte	1 (2%)				
Inflammation, chronic	1 (2%)	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Mixed cell focus	3 (6%)	1 (2%)		1 (2%)	3 (6%)
Mixed cell focus, multiple	1 (2%)		1 (2%)		
Necrosis, focal	1 (2%)	3 (6%)	4 (8%)		5 (10%)
Bile duct, hyperplasia					1 (2%)
Centrilobular, necrosis	2 (4%)				1 (2%)
Hepatocyte, vacuolization cytoplasmic	5 (10%)	5 (10%)	1 (2%)	1 (2%)	3 (6%)
Mesentery	(16)	(10)	(9)	(16)	(5)
Fibrosis			2 (22%)	1 (6%)	
Inflammation, suppurative					1 (20%)
Inflammation, granulomatous				1 (6%)	
Fat, necrosis	11 (69%)	7 (70%)	7 (78%)	12 (75%)	5 (100%)
Oral mucosa	(50)	(50)	(50)	(50)	(50)
Pharyngeal, hyperplasia, squamous, focal			1 (2%)		
Pancreas	(49)	(49)	(50)	(49)	(48)
Atrophy	1 (2%)		1 (2%)	1 (2%)	1 (2%)
Cyst					1 (2%)
Fibrosis			1 (2%)		
Acinus, cytoplasmic alteration		1 (2%)	1 (2%)	9 (18%)	8 (17%)
Salivary glands	(49)	(50)	(49)	(50)	(50)
Atrophy			2 (4%)		
Parotid gland, atrophy		1 (2%)			
Submandibular gland, atrophy		1 (2%)			
Stomach, forestomach	(50)	(50)	(48)	(50)	(48)
Angiectasis				1 (2%)	
Cyst		1 (2%)			
Fibrosis			1 (2%)		
Ulcer				3 (6%)	
Epithelium, hyperplasia	4 (8%)	3 (6%)		3 (6%)	
Stomach, glandular	(50)	(48)	(48)	(50)	(47)
Atrophy, focal					2 (4%)
Cyst	1 (2%)				
Erosion	1 (2%)	1 (2%)			1 (2%)
Erosion, focal					1 (2%)
Hyperplasia, focal				1 (2%)	1 (2%)
Infiltration cellular, polymorphonuclear		1 (2%)			
Ulcer		1 (2%)			1 (2%)
Tongue	(50)	(50)	(50)	(50)	(50)
Cyst		1 (2%)	1 (2%)	1 (2%)	
Hyperplasia, squamous	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic		5 (10%)	4 (8%)	4 (8%)	2 (4%)
Mineralization	1 (2%)	2 (4%)	1 (2%)	2 (4%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Alimentary System (continued)					
Tongue (continued)	(50)	(50)	(50)	(50)	(50)
Ulcer	1 (2%)	2 (4%)			
Artery, inflammation, chronic		1 (2%)	1 (2%)		
Tooth	(1)	(3)		(2)	
Malformation	1 (100%)	2 (67%)		2 (100%)	
Cardiovascular System					
Blood vessel	(2)	(1)	(1)	(1)	(1)
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	45 (90%)	46 (92%)	43 (86%)	46 (92%)	36 (72%)
Inflammation, suppurative	1 (2%)	1 (2%)			
Mineralization	1 (2%)				1 (2%)
Thrombosis		1 (2%)	1 (2%)		3 (6%)
Endocrine System					
Adrenal cortex	(49)	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)				
Angiectasis			1 (2%)		1 (2%)
Degeneration, fatty		1 (2%)			
Hyperplasia, focal			1 (2%)	2 (4%)	2 (4%)
Hypertrophy, focal	7 (14%)	12 (24%)	11 (22%)	13 (26%)	9 (18%)
Capsule, hemorrhage		1 (2%)			
Capsule, hyperplasia	5 (10%)	13 (27%)	11 (22%)	12 (24%)	7 (14%)
Adrenal medulla	(49)	(48)	(50)	(50)	(50)
Hyperplasia			1 (2%)		
Islets, pancreatic	(49)	(49)	(50)	(50)	(49)
Hyperplasia	39 (80%)	40 (82%)	34 (68%)	43 (86%)	20 (41%)
Parathyroid gland	(46)	(47)	(45)	(49)	(47)
Cyst		1 (2%)			1 (2%)
Pituitary gland	(49)	(49)	(48)	(50)	(47)
Pars distalis, cyst	2 (4%)	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Pars distalis, hyperplasia, focal			1 (2%)	1 (2%)	2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)	(50)
Follicle, cyst	1 (2%)	2 (4%)	1 (2%)	3 (6%)	
Follicle, degeneration, focal	3 (6%)	5 (10%)	4 (8%)	5 (10%)	1 (2%)
Follicular cell, hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)		2 (4%)
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(50)	(50)
Degeneration	1 (2%)				
Granuloma sperm			1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocyte			1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)				

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Genital System (continued)					
Preputial gland	(50)	(50)	(50)	(50)	(50)
Atrophy			1 (2%)		
Cyst	2 (4%)	1 (2%)	3 (6%)	4 (8%)	4 (8%)
Infiltration cellular, lymphocyte				1 (2%)	
Inflammation, chronic		1 (2%)			
Prostate	(50)	(49)	(50)	(50)	(50)
Infiltration cellular, lymphocyte		2 (4%)		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)			
Inflammation, chronic	2 (4%)		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)		
Inflammation, chronic	2 (4%)		1 (2%)	1 (2%)	
Epithelium, hyperplasia			1 (2%)		
Testes	(50)	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	2 (4%)	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Interstitial cell, hyperplasia	1 (2%)				
Hematopoietic System					
Bone marrow	(49)	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)	
Hyperplasia		5 (10%)	5 (10%)	1 (2%)	3 (6%)
Pigmentation	47 (96%)	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Lymph node	(8)	(4)	(6)	(6)	(5)
Bronchial, hyperplasia, lymphoid		1 (25%)	1 (17%)		
Iliac, hemorrhage	1 (13%)				
Iliac, hyperplasia, lymphoid	1 (13%)		1 (17%)	2 (33%)	
Iliac, hyperplasia, plasma cell					1 (20%)
Iliac, pigmentation				4 (67%)	1 (20%)
Inguinal, hyperplasia, lymphoid	2 (25%)		1 (17%)		
Inguinal, pigmentation		2 (50%)		1 (17%)	3 (60%)
Mediastinal, hemorrhage					1 (20%)
Mediastinal, hyperplasia, histiocytic			1 (17%)		
Mediastinal, hyperplasia, lymphoid		1 (25%)			
Popliteal, hyperplasia, lymphoid	1 (13%)				
Renal, angiectasis	1 (13%)				
Renal, hyperplasia, lymphoid	2 (25%)			1 (17%)	
Renal, hyperplasia, plasma cell					1 (20%)
Lymph node, mandibular	(47)	(49)	(49)	(48)	(46)
Hyperplasia, lymphoid	6 (13%)	6 (12%)	2 (4%)	4 (8%)	2 (4%)
Pigmentation					2 (4%)
Lymph node, mesenteric	(47)	(47)	(49)	(49)	(46)
Ectasia	3 (6%)				
Fibrosis	1 (2%)				
Hemorrhage		1 (2%)	2 (4%)		
Hyperplasia, lymphoid		4 (9%)	2 (4%)	3 (6%)	
Infiltration cellular, histiocyte	14 (30%)	38 (81%)	31 (63%)	32 (65%)	42 (91%)
Inflammation, granulomatous	2 (4%)		1 (2%)		
Necrosis, lymphoid			1 (2%)		
Lymph node, pancreatic	(5)	(13)	(10)	(8)	(16)
Hyperplasia, lymphoid				1 (13%)	1 (6%)
Infiltration cellular, histiocyte		2 (15%)	2 (20%)	5 (63%)	12 (75%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Hematopoietic System (continued)					
Spleen	(49)	(48)	(49)	(49)	(46)
Hematopoietic cell proliferation	17 (35%)	14 (29%)	13 (27%)	19 (39%)	25 (54%)
Hyperplasia, histiocytic				1 (2%)	
Necrosis, lymphoid				1 (2%)	
Lymphoid follicle, atrophy	1 (2%)	2 (4%)	1 (2%)		3 (7%)
Lymphoid follicle, hyperplasia	1 (2%)	6 (13%)	3 (6%)	5 (10%)	4 (9%)
Thymus	(49)	(50)	(46)	(49)	(40)
Atrophy	2 (4%)	7 (14%)	2 (4%)	2 (4%)	1 (3%)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	1 (2%)	2 (4%)	
Necrosis, lymphoid			1 (2%)		
Integumentary System					
Skin	(50)	(50)	(50)	(50)	(50)
Congestion				1 (2%)	
Cyst				1 (2%)	
Cyst epithelial inclusion		2 (4%)		1 (2%)	1 (2%)
Edema			1 (2%)		1 (2%)
Hyperkeratosis					1 (2%)
Inflammation, granulomatous				1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)			2 (4%)	1 (2%)
Ulcer	1 (2%)			3 (6%)	1 (2%)
Dermis, cyst	1 (2%)				
Epidermis, hyperplasia	1 (2%)			1 (2%)	1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Hyperostosis	1 (2%)				
Cranium, osteopetrosis	1 (2%)	2 (4%)	1 (2%)	1 (2%)	
Skeletal muscle	(4)	(2)	(4)	(1)	
Fibrosis			2 (50%)		
Hemorrhage	1 (25%)				
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)		
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Congestion	1 (2%)				
Infiltration cellular, histiocyte	1 (2%)	6 (12%)	3 (6%)	1 (2%)	
Infiltration cellular, lymphocyte			1 (2%)	1 (2%)	
Inflammation, granulomatous	1 (2%)				
Inflammation, chronic		1 (2%)			
Metaplasia, osseous					2 (4%)
Alveolar epithelium, hyperplasia	4 (8%)	3 (6%)	2 (4%)	5 (10%)	3 (6%)
Nose	(50)	(50)	(50)	(50)	(50)
Glands, inflammation				1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	28.6 mg/L	85.7 mg/L	257.4 mg/L
Special Senses System					
Eye	(48)	(49)	(49)	(50)	(47)
Atrophy	1 (2%)	1 (2%)			
Harderian gland	(50)	(50)	(49)	(50)	(50)
Hyperplasia, focal		1 (2%)			
Urinary System					
Kidney	(50)	(50)	(50)	(50)	(49)
Atrophy					1 (2%)
Cyst	3 (6%)	6 (12%)	4 (8%)	3 (6%)	2 (4%)
Fibrosis			1 (2%)		
Hydronephrosis		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infarct	5 (10%)	1 (2%)	2 (4%)	6 (12%)	4 (8%)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		1 (2%)	4 (8%)
Inflammation, suppurative		1 (2%)		1 (2%)	
Metaplasia, osseous	1 (2%)	1 (2%)		1 (2%)	
Mineralization			1 (2%)		
Nephropathy	39 (78%)	43 (86%)	45 (90%)	45 (90%)	41 (84%)
Thrombosis	1 (2%)				
Papilla, necrosis		1 (2%)			
Renal tubule, atrophy					1 (2%)
Renal tubule, mineralization	1 (2%)	1 (2%)			
Renal tubule, necrosis	1 (2%)				
Renal tubule, pigmentation	7 (14%)	3 (6%)	3 (6%)		
Urethra	(1)	(1)		(1)	
Angiectasis	1 (100%)			1 (100%)	
Urinary bladder	(49)	(50)	(50)	(49)	(46)
Fibrosis			1 (2%)		
Infiltration cellular, lymphocyte		1 (2%)	1 (2%)		1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF SODIUM DICHROMATE DIHYDRATE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	5		2	2	3
Natural deaths	8	11	3	6	5
Survivors					
Died last week of study	2	1	1	2	
Terminal sacrifice	35	38	44	40	42
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Gallbladder	(44)	(47)	(48)	(45)	(50)
Sarcoma, metastatic, mesentery		1 (2%)			
Intestine large, colon	(43)	(43)	(48)	(45)	(48)
Intestine small, duodenum	(42)	(42)	(48)	(42)	(48)
Adenoma			2 (4%)	12 (29%)	6 (13%)
Adenoma, multiple				1 (2%)	6 (13%)
Carcinoma				1 (2%)	6 (13%)
Intestine small, ileum	(42)	(43)	(47)	(44)	(47)
Intestine small, jejunum	(41)	(42)	(48)	(44)	(48)
Adenoma		1 (2%)		2 (5%)	4 (8%)
Adenoma, multiple					1 (2%)
Carcinoma	1 (2%)		2 (4%)	2 (5%)	1 (2%)
Sarcoma, metastatic, mesentery		1 (2%)			
Liver	(49)	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)				
Hemangiosarcoma	1 (2%)	3 (6%)			
Hepatocellular adenoma	6 (12%)	11 (22%)	10 (20%)	5 (10%)	3 (6%)
Hepatocellular adenoma, multiple	8 (16%)	10 (20%)	3 (6%)	1 (2%)	
Hepatocellular carcinoma	7 (14%)	9 (18%)	7 (14%)	6 (12%)	6 (12%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)			1 (2%)
Mesentery	(20)	(23)	(23)	(23)	(9)
Carcinoma, metastatic, Harderian gland			1 (4%)		
Fibrosarcoma	3 (15%)				
Fibrosarcoma, metastatic, skin			1 (4%)		1 (11%)
Granulosa-theca tumor malignant, metastatic, ovary		1 (4%)			
Hemangiosarcoma, metastatic, spleen	1 (5%)				
Liposarcoma, metastatic, skin		1 (4%)			
Sarcoma		2 (9%)	2 (9%)		
Sarcoma, metastatic, skin				1 (4%)	
Pancreas	(48)	(50)	(49)	(50)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)		
Hepatocellular carcinoma, metastatic, liver		1 (2%)			
Sarcoma, metastatic, mesentery		1 (2%)			
Salivary glands	(50)	(50)	(50)	(48)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)			
Stomach, forestomach	(49)	(49)	(50)	(48)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)			3 (6%)
Stomach, glandular	(49)	(48)	(50)	(48)	(50)
Sarcoma, metastatic, mesentery		1 (2%)			
Tongue	(50)	(50)	(49)	(48)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Granulosa-theca tumor malignant, metastatic, ovary		1 (2%)			
Sarcoma, metastatic, mesentery		1 (2%)			
Endocrine System					
Adrenal cortex	(49)	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery		1 (2%)			
Capsule, adenoma			1 (2%)		
Capsule, carcinoma					1 (2%)
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Pheochromocytoma benign		1 (2%)	2 (4%)	1 (2%)	
Islets, pancreatic	(49)	(50)	(50)	(50)	(50)
Adenoma	1 (2%)				
Carcinoma			1 (2%)		
Parathyroid gland	(48)	(49)	(50)	(44)	(49)
Pituitary gland	(48)	(48)	(48)	(48)	(49)
Pars distalis, adenoma	3 (6%)	3 (6%)	2 (4%)	3 (6%)	3 (6%)
Thyroid gland	(50)	(50)	(50)	(49)	(50)
Adenoma				1 (2%)	
Fibrosarcoma, metastatic, skin		1 (2%)			
C-cell, carcinoma				1 (2%)	
Follicular cell, adenoma	1 (2%)		1 (2%)		2 (4%)
Follicular cell, carcinoma				1 (2%)	
General Body System					
Tissue NOS	(1)				
Genital System					
Clitoral gland	(50)	(50)	(50)	(50)	(48)
Sarcoma, metastatic, skin			1 (2%)		1 (2%)
Ovary	(50)	(49)	(47)	(48)	(49)
Cystadenoma	1 (2%)	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Granulosa cell tumor benign		1 (2%)			
Granulosa-theca tumor malignant		1 (2%)			
Hemangioma			1 (2%)		
Hemangiosarcoma			1 (2%)	1 (2%)	
Teratoma benign					1 (2%)
Uterus	(50)	(50)	(50)	(50)	(50)
Hemangiosarcoma				2 (4%)	
Polyp stromal	1 (2%)				
Sarcoma stromal					1 (2%)
Vagina	(1)				
Squamous cell papilloma	1 (100%)				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Lymph node	(10)	(7)	(6)	(5)	(6)
Axillary, sarcoma, metastatic, skin			1 (17%)		
Bronchial, liposarcoma, metastatic, skin		1 (14%)			
Inguinal, sarcoma, metastatic, skin			1 (17%)		
Mediastinal, fibrosarcoma, metastatic, skin		1 (14%)			
Mediastinal, granulosa-theca tumor malignant, metastatic, ovary		1 (14%)			
Mediastinal, liposarcoma, metastatic, skin		1 (14%)			
Mediastinal, sarcoma, metastatic, skin			1 (17%)		
Lymph node, mandibular	(50)	(48)	(49)	(48)	(48)
Carcinoma, metastatic, Harderian gland			1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)			
Lymph node, mesenteric	(46)	(48)	(46)	(50)	(50)
Fibrosarcoma, metastatic, mesentery	1 (2%)				
Sarcoma, metastatic, mesentery		1 (2%)			
Lymph node, pancreatic	(14)	(12)	(15)	(14)	(13)
Granulosa cell tumor malignant, metastatic, ovary		1 (8%)			
Spleen	(48)	(48)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)	
Sarcoma, metastatic, mesentery		1 (2%)			
Sarcoma, metastatic, skin			1 (2%)		
Thymus	(46)	(38)	(43)	(40)	(47)
Integumentary System					
Mammary gland	(50)	(48)	(50)	(50)	(50)
Carcinoma					1 (2%)
Fibroadenoma		1 (2%)			
Skin	(50)	(50)	(50)	(49)	(50)
Fibrosarcoma		1 (2%)			
Hemangioma			1 (2%)		
Squamous cell papilloma			1 (2%)		
Pinna, fibrosarcoma		1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)		1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, liposarcoma		1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Osteoma			1 (2%)		
Osteosarcoma			1 (2%)		
Cranium, osteoma	1 (2%)				
Skeletal muscle	(2)	(6)	(1)	(1)	(1)
Carcinoma, metastatic, Harderian gland			1 (100%)		
Fibrosarcoma, metastatic, skin	1 (50%)	1 (17%)			
Granulosa-theca tumor malignant, metastatic, ovary		1 (17%)			
Liposarcoma, metastatic, skin		1 (17%)			
Sarcoma		1 (17%)			
Sarcoma, metastatic, mesentery		1 (17%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	5 (10%)	7 (14%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	2 (4%)	2 (4%)	1 (2%)	
Carcinoma, metastatic, Harderian gland			1 (2%)		
Fibrosarcoma, metastatic, skin		2 (4%)			
Granulosa-theca tumor malignant, metastatic, ovary		1 (2%)			
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)			1 (2%)
Liposarcoma, metastatic, skin		1 (2%)			
Sarcoma, metastatic, skin			1 (2%)		
Nose	(50)	(50)	(50)	(50)	(50)
Carcinoma, metastatic, Harderian gland			1 (2%)		
Special Senses System					
Eye	(49)	(48)	(48)	(46)	(50)
Harderian gland	(49)	(49)	(50)	(50)	(50)
Adenoma	4 (8%)	5 (10%)	5 (10%)	7 (14%)	5 (10%)
Carcinoma	1 (2%)		1 (2%)		1 (2%)
Urinary System					
Kidney	(50)	(49)	(50)	(49)	(50)
Ureter				(1)	
Urinary bladder	(50)	(48)	(50)	(48)	(49)
Systemic Lesions					
Multiple organs[b]	(50)	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)		1 (2%)	1 (2%)
Lymphoma malignant	7 (14%)	3 (6%)	2 (4%)	5 (10%)	5 (10%)
Neoplasm Summary					
Total animals with primary neoplasms[c]	36	37	37	39	38
Total primary neoplasms	58	71	62	61	65
Total animals with benign neoplasms	27	28	27	25	29
Total benign neoplasms	30	43	40	37	38
Total animals with malignant neoplasms	22	23	19	21	18
Total malignant neoplasms	28	28	22	24	27
Total animals with metastatic neoplasms	5	6	3	1	3
Total metastatic neoplasms	5	29	13	1	3

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

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Harderian Gland: Adenoma					
Overall rate[a]	4/50 (8%)	5/50 (10%)	5/50 (10%)	7/50 (14%)	5/50 (10%)
Adjusted rate[b]	8.9%	10.8%	10.4%	15.0%	10.6%
Terminal rate[c]	4/37 (11%)	4/39 (10%)	5/45 (11%)	7/42 (17%)	5/42 (12%)
First incidence (days)	729 (T)	671	729 (T)	729 (T)	729 (T)
Poly-3 test[d]	P=0.516	P=0.517	P=0.538	P=0.283	P=0.531
Harderian Gland: Adenoma or Carcinoma					
Overall rate	5/50 (10%)	5/50 (10%)	6/50 (12%)	7/50 (14%)	6/50 (12%)
Adjusted rate	11.0%	10.8%	12.4%	15.0%	12.7%
Terminal rate	4/37 (11%)	4/39 (10%)	5/45 (11%)	7/42 (17%)	6/42 (14%)
First incidence (days)	583	671	611	729 (T)	729 (T)
Poly-3 test	P=0.462	P=0.620N	P=0.541	P=0.398	P=0.527
Small Intestine (Duodenum): Adenoma					
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	13/50 (26%)	12/50 (24%)
Adjusted rate	0.0%	0.0%	4.2%	27.8%	25.2%
Terminal rate	0/37 (0%)	0/39 (0%)	2/45 (4%)	13/42 (31%)	11/42 (26%)
First incidence (days)	—[e]	—[f]	729 (T)	729 (T)	693
Poly-3 test	P<0.001		P=0.251	P<0.001	P<0.001
Small Intestine (Duodenum): Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted rate	0.0%	0.0%	0.0%	2.1%	12.6%
Terminal rate	0/37 (0%)	0/39 (0%)	0/45 (0%)	1/42 (2%)	5/42 (12%)
First incidence (days)	—	—	—	729 (T)	625
Poly-3 test	P<0.001	—	—	P=0.507	P=0.019
Small Intestine (Jejunum): Adenoma					
Overall rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	2.2%	0.0%	4.3%	10.6%
Terminal rate	0/37 (0%)	1/39 (3%)	0/45 (0%)	2/42 (5%)	5/42 (12%)
First incidence (days)	—	729 (T)	—	729 (T)	729 (T)
Poly-3 test	P=0.002	P=0.504	—	P=0.246	P=0.035
Small Intestine (Duodenum, Jejunum, or Ileum): Adenoma					
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	15/50 (30%)	16/50 (32%)
Adjusted rate	0.0%	2.2%	4.2%	32.0%	33.7%
Terminal rate	0/37 (0%)	1/39 (3%)	2/45 (4%)	15/42 (36%)	15/42 (36%)
First incidence (days)	—	729 (T)	729 (T)	729 (T)	693
Poly-3 test	P<0.001	P=0.504	P=0.251	P<0.001	P<0.001
Small Intestine (Duodenum, Jejunum, or Ileum): Carcinoma					
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted rate	2.2%	0.0%	4.2%	6.4%	14.7%
Terminal rate	1/37 (3%)	0/39 (0%)	2/45 (4%)	3/42 (7%)	6/42 (14%)
First incidence (days)	729 (T)	—	729 (T)	729 (T)	625
Poly-3 test	P<0.001	P=0.496N	P=0.521	P=0.319	P=0.037

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Small Intestine (Duodenum, Jejunum, or Ileum): Adenoma or Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	17/50 (34%)	22/50 (44%)
Adjusted rate	2.2%	2.2%	8.3%	36.3%	45.9%
Terminal rate	1/37 (3%)	1/39 (3%)	4/45 (9%)	17/42 (41%)	20/42 (48%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)	625
Poly-3 test	P<0.001	P=0.756N	P=0.198	P<0.001	P<0.001
Liver: Hemangiosarcoma					
Overall rate	1/49 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.2%	6.5%	0.0%	0.0%	0.0%
Terminal rate	0/37 (0%)	2/39 (5%)	0/45 (0%)	0/42 (0%)	0/42 (0%)
First incidence (days)	668	688	—	—	—
Poly-3 test	P=0.149N	P=0.313	P=0.489N	P=0.494N	P=0.491N
Liver: Hepatocellular Adenoma					
Overall rate	14/49 (29%)	21/50 (42%)	13/50 (26%)	6/50 (12%)	3/50 (6%)
Adjusted rate	31.0%	45.5%	27.1%	12.8%	6.3%
Terminal rate	13/37 (35%)	21/39 (54%)	13/45 (29%)	6/42 (14%)	3/42 (7%)
First incidence (days)	696	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P<0.001N	P=0.109	P=0.429N	P=0.029N	P=0.002N
Liver: Hepatocellular Carcinoma					
Overall rate	8/49 (16%)	10/50 (20%)	7/50 (14%)	6/50 (12%)	7/50 (14%)
Adjusted rate	17.7%	21.3%	14.6%	12.7%	14.6%
Terminal rate	7/37 (19%)	7/39 (18%)	7/45 (16%)	5/42 (12%)	4/42 (10%)
First incidence (days)	696	629	729 (T)	555	664
Poly-3 test	P=0.327N	P=0.432	P=0.451N	P=0.351N	P=0.452N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	17/49 (35%)	25/50 (50%)	17/50 (34%)	10/50 (20%)	10/50 (20%)
Adjusted rate	37.6%	53.2%	35.5%	21.1%	20.9%
Terminal rate	16/37 (43%)	22/39 (56%)	17/45 (38%)	9/42 (21%)	7/42 (17%)
First incidence (days)	696	629	729 (T)	555	664
Poly-3 test	P=0.003N	P=0.094	P=0.501N	P=0.062N	P=0.058N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	1/50 (2%)	5/50 (10%)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.2%	10.8%	14.6%	4.3%	4.2%
Terminal rate	1/37 (3%)	5/39 (13%)	6/45 (13%)	2/42 (5%)	1/42 (2%)
First incidence (days)	729 (T)	729 (T)	722	729 (T)	625
Poly-3 test	P=0.205N	P=0.106	P=0.037	P=0.513	P=0.520
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	2/50 (4%)	7/50 (14%)	9/50 (18%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.4%	15.2%	18.8%	6.4%	4.2%
Terminal rate	2/37 (5%)	7/39 (18%)	8/45 (18%)	2/42 (5%)	1/42 (2%)
First incidence (days)	729 (T)	729 (T)	722	599	625
Poly-3 test	P=0.075N	P=0.084	P=0.032	P=0.521	P=0.673N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Mesentery: Fibrosarcoma					
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.6%	0.0%	0.0%	0.0%	0.0%
Terminal rate	2/37 (5%)	0/39 (0%)	0/45 (0%)	0/42 (0%)	0/42 (0%)
First incidence (days)	655	—	—	—	—
Poly-3 test	P=0.197N	P=0.116N	P=0.109N	P=0.113N	P=0.111N
Ovary: Cystadenoma					
Overall rate	1/50 (2%)	3/49 (6%)	3/47 (6%)	2/48 (4%)	2/49 (4%)
Adjusted rate	2.2%	6.7%	6.7%	4.4%	4.3%
Terminal rate	0/37 (0%)	3/38 (8%)	3/42 (7%)	2/41 (5%)	2/41 (5%)
First incidence (days)	695	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.541N	P=0.304	P=0.303	P=0.500	P=0.509
Pituitary Gland (Pars Distalis): Adenoma					
Overall rate	3/48 (6%)	3/48 (6%)	2/48 (4%)	3/48 (6%)	3/49 (6%)
Adjusted rate	6.7%	6.8%	4.3%	6.7%	6.5%
Terminal rate	1/37 (3%)	3/37 (8%)	2/44 (5%)	3/41 (7%)	3/41 (7%)
First incidence (days)	552	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.559	P=0.652	P=0.488N	P=0.659	P=0.649N
Skin: Fibrosarcoma or Sarcoma					
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.4%	6.4%	4.2%	4.2%	6.3%
Terminal rate	1/37 (3%)	2/39 (5%)	2/45 (4%)	1/42 (2%)	1/42 (2%)
First incidence (days)	695	461	729 (T)	646	646
Poly-3 test	P=0.484	P=0.516	P=0.673N	P=0.679N	P=0.526
Stomach (Forestomach): Squamous Cell Papilloma					
Overall rate	1/50 (2%)	2/50 (4%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.2%	4.3%	0.0%	0.0%	6.3%
Terminal rate	0/37 (0%)	2/39 (5%)	0/45 (0%)	0/42 (0%)	3/42 (7%)
First incidence (days)	616	729 (T)	—	—	729 (T)
Poly-3 test	P=0.145	P=0.505	P=0.490N	P=0.494N	P=0.320
All Organs: Hemangiosarcoma					
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	4.4%	6.5%	4.2%	8.5%	0.0%
Terminal rate	0/37 (0%)	2/39 (5%)	2/45 (4%)	3/42 (7%)	0/42 (0%)
First incidence (days)	583	688	729 (T)	646	—
Poly-3 test	P=0.140N	P=0.505	P=0.677N	P=0.350	P=0.230N
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted rate	6.6%	6.5%	8.3%	8.5%	0.0%
Terminal rate	1/37 (3%)	2/39 (5%)	4/45 (9%)	3/42 (7%)	0/42 (0%)
First incidence (days)	583	688	729 (T)	646	—
Poly-3 test	P=0.072N	P=0.658N	P=0.524	P=0.515	P=0.113N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
All Organs: Malignant Lymphoma					
Overall rate	7/50 (14%)	3/50 (6%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate	15.3%	6.4%	4.2%	10.4%	10.5%
Terminal rate	4/37 (11%)	1/39 (3%)	2/45 (4%)	2/42 (5%)	4/42 (10%)
First incidence (days)	616	632	729 (T)	428	652
Poly-3 test	P=0.472	P=0.149N	P=0.068N	P=0.346N	P=0.351N
All Organs: Benign Neoplasms					
Overall rate	27/50 (54%)	28/50 (56%)	27/50 (54%)	25/50 (50%)	29/50 (58%)
Adjusted rate	56.6%	60.4%	55.9%	53.4%	59.3%
Terminal rate	21/37 (57%)	26/39 (67%)	25/45 (56%)	25/42 (60%)	26/42 (62%)
First incidence (days)	212	671	646	729 (T)	170
Poly-3 test	P=0.479	P=0.434	P=0.555N	P=0.457N	P=0.475
All Organs: Malignant Neoplasms					
Overall rate	22/50 (44%)	23/50 (46%)	19/50 (38%)	21/50 (42%)	18/50 (36%)
Adjusted rate	46.7%	47.1%	38.2%	42.5%	36.8%
Terminal rate	15/37 (41%)	14/39 (36%)	15/45 (33%)	14/42 (33%)	12/42 (29%)
First incidence (days)	583	461	311	428	625
Poly-3 test	P=0.202N	P=0.564	P=0.262N	P=0.417N	P=0.220N
All Organs: Benign or Malignant Neoplasms					
Overall rate	36/50 (72%)	37/50 (74%)	37/50 (74%)	39/50 (78%)	38/50 (76%)
Adjusted rate	73.4%	75.8%	74.0%	79.0%	76.2%
Terminal rate	26/37 (70%)	28/39 (72%)	32/45 (71%)	32/42 (76%)	31/42 (74%)
First incidence (days)	212	461	311	428	170
Poly-3 test	P=0.441	P=0.484	P=0.566	P=0.342	P=0.465

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

TABLE D3
Historical Incidence of Small Intestine Neoplasms in Control Female B6C3F1 Mice[a]

Study	Incidence in Controls						
	Duodenum		Jejunum		Duodenum, Jejunum, or Ileum		
	Adenoma	Carcinoma	Adenoma	Carcinoma	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence: Drinking Water Studies							
Bromochloroacetic acid	1/50	0/50	0/50	1/50	1/50	1/50	2/50
Bromodichloromethane	0/50	0/50	0/50	0/50	0/50	1/50	1/50
Dibromoacetic acid	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Dibromoacetonitrile	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Dipropylene glycol	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Sodium chlorate	0/50	0/50	0/50	0/50	0/50	0/50	0/50
Sodium dichromate dihydrate	0/50	0/50	0/50	1/50	0/50	1/50	1/50
Overall Historical Incidence: Drinking Water Studies							
Total (%)	1/350 (0.3%)	0/350	0/350	2/350 (0.6%)	1/350 (0.3%)	3/350 (0.9%)	4/350 (1.1%)
Mean ± standard deviation	0.3% ± 0.8%			0.6% ± 1.0%	0.3% ± 0.8%	0.9% ± 1.1%	1.1% ± 1.6%
Range	(0%-2%)			(0%-2%)	(0%-2%)	(0%-2%)	(0%-4%)
Overall Historical Incidence: All Routes							
Total (%)	3/1,648 (0.2%)	1/1,648 (0.1%)	0/1,648	5/1,648 (0.3%)	3/1,648 (0.2%)	8/1,648 (0.5%)	11/1,648 (0.7%)
Mean ± standard deviation	0.2% ± 0.6%	0.1% ± 0.4%		0.3% ± 0.7%	0.2% ± 0.6%	0.5% ± 0.8%	0.7% ± 1.1%
Range	(0%-2%)	(0%-2%)		(0%-2%)	(0%-2%)	(0%-2%)	(0%-4%)

[a] Data as of March 2, 2007, with sodium dichromate dihydrate data added from Table D1

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Disposition Summary					
Animals initially in study	50	50	50	50	50
Early deaths					
Moribund	5		2	2	3
Natural deaths	8	11	3	6	5
Survivors					
Died last week of study	2	1	1	2	
Terminal sacrifice	35	38	44	40	42
Animals examined microscopically	50	50	50	50	50
Alimentary System					
Gallbladder	(44)	(47)	(48)	(45)	(50)
Intestine large, colon	(43)	(43)	(48)	(45)	(48)
Edema		1 (2%)			
Lymphoid tissue, hyperplasia	2 (5%)	3 (7%)	1 (2%)	1 (2%)	2 (4%)
Intestine small, duodenum	(42)	(42)	(48)	(42)	(48)
Cyst				1 (2%)	
Dilatation					1 (2%)
Hyperplasia, lymphoid	1 (2%)				
Infiltration cellular, histiocyte			4 (8%)	33 (79%)	40 (83%)
Epithelium, hyperplasia, focal			1 (2%)	2 (5%)	
Epithelium, hyperplasia, diffuse		16 (38%)	35 (73%)	31 (74%)	42 (88%)
Lymphoid tissue, hyperplasia			1 (2%)	1 (2%)	2 (4%)
Intestine small, ileum	(42)	(43)	(47)	(44)	(47)
Inflammation, suppurative		1 (2%)			
Intestine small, jejunum	(41)	(42)	(48)	(44)	(48)
Fibrosis			1 (2%)		
Infiltration cellular, histiocyte				2 (5%)	8 (17%)
Inflammation, suppurative		4 (10%)		1 (2%)	1 (2%)
Epithelium, hyperplasia, focal			1 (2%)	1 (2%)	
Epithelium, hyperplasia, diffuse		2 (5%)	1 (2%)		8 (17%)
Lymphoid tissue, hyperplasia	6 (15%)	6 (14%)	6 (13%)	4 (9%)	3 (6%)
Liver	(49)	(50)	(50)	(50)	(50)
Basophilic focus	3 (6%)	4 (8%)	2 (4%)		1 (2%)
Basophilic focus, multiple			2 (4%)		
Clear cell focus	3 (6%)	5 (10%)		2 (4%)	1 (2%)
Cyst	1 (2%)	1 (2%)			
Cyst, multiple	1 (2%)				
Eosinophilic focus	11 (22%)	13 (26%)	5 (10%)	4 (8%)	4 (8%)
Eosinophilic focus, multiple	3 (6%)	5 (10%)	3 (6%)	1 (2%)	
Hematopoietic cell proliferation	3 (6%)		1 (2%)		1 (2%)
Hemorrhage	1 (2%)	2 (4%)			
Infiltration cellular, histiocyte	2 (4%)	15 (30%)	23 (46%)	32 (64%)	45 (90%)
Infiltration cellular, lymphocyte	2 (4%)		1 (2%)		2 (4%)
Inflammation, chronic	16 (33%)	21 (42%)	22 (44%)	27 (54%)	24 (48%)
Mixed cell focus	2 (4%)		4 (8%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)	1 (2%)		2 (4%)	1 (2%)
Tension lipidosis			1 (2%)	1 (2%)	
Thrombosis					1 (2%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)	5 (10%)	5 (10%)		2 (4%)

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Alimentary System (continued)					
Mesentery	(20)	(23)	(23)	(23)	(9)
Fibrosis				1 (4%)	
Hemorrhage					1 (11%)
Inflammation, granulomatous		1 (4%)			
Inflammation, chronic				1 (4%)	1 (11%)
Fat, hemorrhage				1 (4%)	
Fat, necrosis	16 (80%)	20 (87%)	20 (87%)	21 (91%)	6 (67%)
Pancreas	(48)	(50)	(49)	(50)	(50)
Atrophy	1 (2%)			1 (2%)	2 (4%)
Cyst		1 (2%)		1 (2%)	
Necrosis	1 (2%)				
Acinus, atrophy					2 (4%)
Acinus, cytoplasmic alteration		6 (12%)	6 (12%)	14 (28%)	32 (64%)
Acinus, hyperplasia, focal				1 (2%)	
Salivary glands	(50)	(50)	(50)	(48)	(49)
Atrophy			1 (2%)		
Fibrosis				1 (2%)	
Infiltration cellular, lymphocyte	1 (2%)				1 (2%)
Inflammation, chronic	2 (4%)				
Submandibular gland, atrophy	1 (2%)				
Stomach, forestomach	(49)	(49)	(50)	(48)	(50)
Cyst			2 (4%)		
Diverticulum				1 (2%)	
Edema	1 (2%)		1 (2%)		
Erosion		1 (2%)			
Infiltration cellular, lymphocyte		1 (2%)			
Inflammation, chronic					1 (2%)
Mineralization					2 (4%)
Ulcer	3 (6%)	1 (2%)	1 (2%)		2 (4%)
Epithelium, hyperplasia	2 (4%)	2 (4%)		2 (4%)	3 (6%)
Stomach, glandular	(49)	(48)	(50)	(48)	(50)
Cyst	1 (2%)				1 (2%)
Degeneration, cystic			1 (2%)		
Erosion	2 (4%)			1 (2%)	
Fibrosis		1 (2%)			
Infiltration cellular, mixed cell					1 (2%)
Inflammation, suppurative		1 (2%)			
Ulcer		1 (2%)			
Glands, hyperplasia	1 (2%)				
Tongue	(50)	(50)	(49)	(48)	(50)
Inflammation, chronic	7 (14%)	6 (12%)	3 (6%)	5 (10%)	5 (10%)
Mineralization	1 (2%)			1 (2%)	2 (4%)
Artery, inflammation, chronic	1 (2%)		3 (6%)		
Cardiovascular System					
Heart	(50)	(50)	(50)	(50)	(50)
Cardiomyopathy	40 (80%)	34 (68%)	43 (86%)	42 (84%)	43 (86%)
Mineralization	1 (2%)				
Artery, inflammation, chronic	1 (2%)				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Endocrine System					
Adrenal cortex	(49)	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	3 (6%)		1 (2%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)				1 (2%)
Hyperplasia, focal			1 (2%)	1 (2%)	1 (2%)
Hyperplasia, diffuse		1 (2%)			1 (2%)
Hypertrophy, focal		2 (4%)	1 (2%)	1 (2%)	
Vacuolization cytoplasmic				1 (2%)	1 (2%)
Capsule, hyperplasia	10 (20%)	4 (8%)	6 (12%)	9 (18%)	14 (28%)
Adrenal medulla	(49)	(50)	(50)	(50)	(50)
Hyperplasia			1 (2%)	1 (2%)	1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)	(50)
Hyperplasia	10 (20%)	5 (10%)	3 (6%)	5 (10%)	7 (14%)
Parathyroid gland	(48)	(49)	(50)	(44)	(49)
Cyst		1 (2%)			1 (2%)
Pituitary gland	(48)	(48)	(48)	(48)	(49)
Pars distalis, angiectasis		1 (2%)			
Pars distalis, cyst				1 (2%)	
Pars distalis, hyperplasia, focal	5 (10%)	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Pars intermedia, fibrosis	1 (2%)				
Rathke's cleft, cyst		1 (2%)		1 (2%)	
Thyroid gland	(50)	(50)	(50)	(49)	(50)
Infiltration cellular, lymphocyte	1 (2%)		1 (2%)		
Infiltration cellular, mixed cell	1 (2%)	2 (4%)			
Inflammation, suppurative, focal				1 (2%)	
Inflammation, chronic				1 (2%)	
Follicle, cyst	2 (4%)	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Follicle, degeneration, focal	12 (24%)	11 (22%)	14 (28%)	10 (20%)	11 (22%)
Follicular cell, hyperplasia					1 (2%)
Follicular cell, hyperplasia, focal		1 (2%)	1 (2%)		2 (4%)
Follicular cell, hypertrophy					1 (2%)
General Body System					
Tissue NOS	(1)				
Genital System					
Clitoral gland	(50)	(50)	(50)	(50)	(48)
Cyst	1 (2%)		1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)	
Ovary	(50)	(49)	(47)	(48)	(49)
Angiectasis		1 (2%)	1 (2%)	1 (2%)	2 (4%)
Atrophy	1 (2%)				2 (4%)
Cyst	10 (20%)	13 (27%)	12 (26%)	11 (23%)	10 (20%)
Hematocyst				1 (2%)	
Hemorrhage	1 (2%)	9 (18%)	2 (4%)	4 (8%)	3 (6%)
Hyperplasia					1 (2%)
Infiltration cellular, lymphocyte	1 (2%)				
Mineralization					1 (2%)
Thrombosis					1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Genital System (continued)					
Uterus	(50)	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	1 (2%)	
Hyperplasia, cystic	43 (86%)	45 (90%)	42 (84%)	43 (86%)	45 (90%)
Inflammation, suppurative	1 (2%)				
Serosa, cyst	1 (2%)				
Vagina	(1)				
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(50)	(50)
Fibrosis					1 (2%)
Hemorrhage				1 (2%)	
Hyperplasia	5 (10%)	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Hyperplasia, reticulum cell				1 (2%)	
Pigmentation	47 (94%)	47 (94%)	49 (98%)	49 (98%)	50 (100%)
Lymph node	(10)	(7)	(6)	(5)	(6)
Bronchial, hyperplasia, lymphoid	1 (10%)	1 (14%)	1 (17%)		
Iliac, hematopoietic cell proliferation	1 (10%)				
Iliac, hyperplasia, lymphoid	1 (10%)		2 (33%)	1 (20%)	1 (17%)
Iliac, pigmentation	1 (10%)				
Mediastinal, hyperplasia, lymphoid	4 (40%)	1 (14%)	2 (33%)		1 (17%)
Renal, hyperplasia, lymphoid			2 (33%)		
Lymph node, mandibular	(50)	(48)	(49)	(48)	(48)
Ectasia	1 (2%)				
Hyperplasia, lymphoid	4 (8%)	2 (4%)	4 (8%)	6 (13%)	3 (6%)
Lymph node, mesenteric	(46)	(48)	(46)	(50)	(50)
Ectasia	6 (13%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)		
Hemorrhage			1 (2%)		1 (2%)
Hyperplasia, lymphoid	3 (7%)	4 (8%)	6 (13%)	4 (8%)	2 (4%)
Infiltration cellular, histiocyte	3 (7%)	29 (60%)	26 (57%)	40 (80%)	42 (84%)
Mineralization				1 (2%)	
Lymph, node, pancreatic	(14)	(12)	(15)	(14)	(13)
Hyperplasia, lymphoid	1 (7%)	1 (8%)	2 (13%)		1 (8%)
Infiltration cellular, histiocyte		1 (8%)	2 (13%)	7 (50%)	8 (62%)
Spleen	(48)	(48)	(50)	(50)	(50)
Hematopoietic cell proliferation	15 (31%)	24 (50%)	19 (38%)	15 (30%)	15 (30%)
Necrosis				1 (2%)	
Lymphoid follicle, atrophy		1 (2%)			
Lymphoid follicle, hyperplasia	17 (35%)	19 (40%)	28 (56%)	22 (44%)	18 (36%)
Thymus	(46)	(38)	(43)	(40)	(47)
Angiectasis				1 (3%)	
Atrophy	2 (4%)			1 (3%)	1 (2%)
Hyperplasia, lymphoid	30 (65%)	20 (53%)	17 (40%)	25 (63%)	32 (68%)
Integumentary System					
Mammary gland	(50)	(48)	(50)	(50)	(50)
Cyst	3 (6%)				1 (2%)
Hyperplasia				1 (2%)	1 (2%)
Duct, cyst				1 (2%)	
Skin	(50)	(50)	(50)	(49)	(50)
Edema			1 (2%)		
Inflammation, granulomatous	1 (2%)				
Inflammation, chronic			1 (2%)		
Ulcer		1 (2%)	1 (2%)	1 (2%)	
Dermis, cyst	1 (2%)				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Musculoskeletal System					
Bone	(50)	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)		
Cranium, fibrosis					1 (2%)
Cranium, osteopetrosis	1 (2%)	1 (2%)			
Skeletal muscle	(2)	(6)	(1)	(1)	(1)
Fibrosis					1 (100%)
Nervous System					
Brain	(50)	(50)	(50)	(50)	(50)
Compression	1 (2%)		2 (4%)	2 (4%)	
Cerebellum, vacuolization cytoplasmic	1 (2%)				
Cerebrum, edema	1 (2%)				
Respiratory System					
Lung	(50)	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)				
Hemorrhage		1 (2%)		1 (2%)	
Infiltration cellular, histiocyte	2 (4%)		2 (4%)		2 (4%)
Infiltration cellular, lymphocyte	1 (2%)	4 (8%)	6 (12%)	4 (8%)	5 (10%)
Infiltration cellular, mixed cell				1 (2%)	
Metaplasia, osseous	1 (2%)				
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)		1 (2%)
Capillary, infiltration cellular, mixed cell					1 (2%)
Nose	(50)	(50)	(50)	(50)	(50)
Special Senses System					
Eye	(49)	(48)	(48)	(46)	(50)
Atrophy				1 (2%)	1 (2%)
Harderian gland	(49)	(49)	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)	
Urinary System					
Kidney	(50)	(49)	(50)	(49)	(50)
Accumulation, hyaline droplet			1 (2%)		
Calculus microscopic observation only		4 (8%)		3 (6%)	5 (10%)
Casts protein				1 (2%)	
Cyst		2 (4%)			1 (2%)
Hemorrhage		1 (2%)			1 (2%)
Hydronephrosis		1 (2%)		2 (4%)	1 (2%)
Infarct	4 (8%)		3 (6%)	2 (4%)	2 (4%)
Infiltration cellular			1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, lymphocyte	10 (20%)	5 (10%)	10 (20%)	10 (20%)	7 (14%)
Inflammation, chronic		1 (2%)	2 (4%)		
Metaplasia, osseous	1 (2%)	1 (2%)		3 (6%)	1 (2%)
Mineralization		2 (4%)			1 (2%)
Nephropathy	21 (42%)	30 (61%)	30 (60%)	26 (53%)	28 (56%)
Papilla, necrosis			1 (2%)		1 (2%)
Renal tubule, accumulation, hyaline droplet					1 (2%)
Renal tubule, mineralization	1 (2%)				
Renal tubule, pigmentation					1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Urinary System (continued)					
Ureter				(1)	
Urinary bladder	(50)	(48)	(50)	(48)	(49)
Infiltration cellular, lymphocyte	42 (84%)	33 (69%)	37 (74%)	27 (56%)	38 (78%)

APPENDIX E
CLINICAL PATHOLOGY RESULTS

TABLE E1
Hematology and Clinical Chemistry Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematology					
n					
Day 4	9	10	9	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	8	10
Hematocrit (auto) (%)					
Day 4	37.5 ± 0.5	37.7 ± 0.5	36.4 ± 0.8	35.8 ± 0.7	37.0 ± 0.6
Day 22	46.5 ± 0.9	45.3 ± 0.5	44.2 ± 0.7	38.4 ± 0.8**	28.0 ± 0.6**
Month 3	45.1 ± 0.3	44.6 ± 0.4	44.7 ± 0.5	44.6 ± 0.5	43.0 ± 0.5**
Month 6	46.5 ± 0.3	46.7 ± 0.5	46.3 ± 0.5	46.5 ± 0.4	46.0 ± 0.3
Month 12	48.8 ± 0.6	48.0 ± 0.4	48.8 ± 0.7	49.3 ± 0.5	48.6 ± 0.4
Hematocrit (spun) (%)					
Day 4	38.2 ± 0.5[b]	38.4 ± 0.6	36.7 ± 0.9	36.4 ± 0.6	37.3 ± 0.6
Day 22	46.0 ± 1.1	44.4 ± 0.4	43.2 ± 0.6*	38.7 ± 0.6**	33.5 ± 0.8**
Month 3	45.3 ± 0.4	44.5 ± 0.3	44.5 ± 0.4	44.1 ± 0.5	41.0 ± 0.5**
Month 6	45.9 ± 0.4	45.7 ± 0.5	45.5 ± 0.4	45.5 ± 0.5	45.0 ± 0.3
Month 12	47.6 ± 0.5	46.6 ± 0.4	47.4 ± 0.5	47.7 ± 0.4	47.3 ± 0.4
Hemoglobin (g/dL)					
Day 4	12.9 ± 0.2	13.0 ± 0.2	12.5 ± 0.3	12.3 ± 0.2	12.8 ± 0.2
Day 22	15.5 ± 0.3	15.1 ± 0.2	14.2 ± 0.2**	12.0 ± 0.3**	10.1 ± 0.2**
Month 3	15.1 ± 0.1	14.9 ± 0.1	14.9 ± 0.2	14.6 ± 0.2*	12.9 ± 0.2**
Month 6	15.2 ± 0.1	15.2 ± 0.2	15.0 ± 0.2	14.9 ± 0.1	14.5 ± 0.1**
Month 12	15.8 ± 0.2	15.4 ± 0.2	15.6 ± 0.2	15.6 ± 0.2	15.3 ± 0.1*
Erythrocytes (10^6/µL)					
Day 4	6.75 ± 0.11	6.80 ± 0.10	6.67 ± 0.17	6.73 ± 0.11	6.98 ± 0.12
Day 22	7.80 ± 0.13	7.74 ± 0.15	8.06 ± 0.16	8.10 ± 0.14	6.21 ± 0.13**
Month 3	9.28 ± 0.05	9.24 ± 0.06	9.46 ± 0.11	9.75 ± 0.11**	10.93 ± 0.16**
Month 6	9.34 ± 0.06	9.43 ± 0.08	9.54 ± 0.11	9.71 ± 0.08**	10.15 ± 0.13**
Month 12	9.27 ± 0.10	9.17 ± 0.07	9.40 ± 0.12	9.61 ± 0.11	9.74 ± 0.08**
Reticulocytes (auto) (10^6/µL)					
Day 4	0.62 ± 0.04	0.56 ± 0.04	0.50 ± 0.04	0.24 ± 0.02**	0.19 ± 0.02**
Day 22	0.38 ± 0.03	0.34 ± 0.02	0.38 ± 0.03	0.43 ± 0.04	0.63 ± 0.07**
Month 3	0.23 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.30 ± 0.01**
Month 6	0.24 ± 0.00	0.22 ± 0.01	0.22 ± 0.01	0.24 ± 0.01	0.24 ± 0.01
Month 12	0.23 ± 0.01	0.23 ± 0.01	0.24 ± 0.01	0.26 ± 0.02	0.23 ± 0.01
Reticulocytes (manual) (10^6/µL)					
Day 4	0.30 ± 0.06	0.29 ± 0.03	0.29 ± 0.06	0.30 ± 0.03	0.27 ± 0.02
Day 22	0.32 ± 0.04	0.27 ± 0.03	0.30 ± 0.03	0.41 ± 0.05	0.52 ± 0.04**
Month 3	0.12 ± 0.02	0.14 ± 0.02	0.10 ± 0.02	0.11 ± 0.03	0.13 ± 0.02
Month 12	0.19 ± 0.02	0.18 ± 0.01	0.21 ± 0.02	0.22 ± 0.03	0.17 ± 0.01
Nucleated erythrocytes (10^3/µL)					
Day 4	0.50 ± 0.17[b]	0.60 ± 0.22	0.20 ± 0.13[b]	0.50 ± 0.17	0.10 ± 0.10
Day 22	0.20 ± 0.13	0.20 ± 0.13	0.30 ± 0.15	0.30 ± 0.21	1.40 ± 0.22**
Month 3	0.20 ± 0.13	0.40 ± 0.22	0.30 ± 0.21	0.20 ± 0.13	0.00 ± 0.00
Month 6	0.30 ± 0.15	0.10 ± 0.10	0.20 ± 0.13	0.10 ± 0.10	0.40 ± 0.22
Month 12	0.30 ± 0.21	0.30 ± 0.21	0.10 ± 0.10	0.38 ± 0.26	0.10 ± 0.10

TABLE E1
Hematology and Clinical Chemistry Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematology (continued)					
n					
Day 4	9	10	9	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	8	10
Mean cell volume (fL)					
Day 4	55.6 ± 0.3	55.5 ± 0.3	54.6 ± 0.3	53.3 ± 0.1**	53.0 ± 0.2**
Day 22	59.5 ± 0.4	58.6 ± 0.5	54.9 ± 0.5**	47.4 ± 0.4**	45.0 ± 0.7**
Month 3	48.6 ± 0.2	48.3 ± 0.2	47.3 ± 0.2**	45.7 ± 0.2**	39.2 ± 0.6**
Month 6	49.8 ± 0.1	49.5 ± 0.1	48.6 ± 0.1**	47.8 ± 0.2**	45.4 ± 0.5**
Month 12	52.6 ± 0.2	52.4 ± 0.2	51.9 ± 0.3	51.4 ± 0.3**	49.9 ± 0.2**
Mean cell hemoglobin (pg)					
Day 4	19.1 ± 0.1	19.1 ± 0.1	18.7 ± 0.1*	18.3 ± 0.1**	18.4 ± 0.1**
Day 22	19.8 ± 0.1	19.5 ± 0.2	17.7 ± 0.2**	14.8 ± 0.2**	16.3 ± 0.5**
Month 3	16.2 ± 0.1	16.2 ± 0.1	15.7 ± 0.0**	15.0 ± 0.1**	11.9 ± 0.3**
Month 6	16.3 ± 0.1	16.1 ± 0.1	15.7 ± 0.1**	15.3 ± 0.1**	14.3 ± 0.2**
Month 12	17.0 ± 0.1	16.8 ± 0.1	16.6 ± 0.1*	16.2 ± 0.1**	15.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)					
Day 4	34.4 ± 0.2	34.4 ± 0.2	34.3 ± 0.2	34.4 ± 0.2	34.7 ± 0.2
Day 22	33.3 ± 0.1	33.3 ± 0.1	32.2 ± 0.2	31.2 ± 0.2**	36.2 ± 0.8
Month 3	33.4 ± 0.1	33.5 ± 0.2	33.2 ± 0.1	32.7 ± 0.1**	30.2 ± 0.3**
Month 6	32.7 ± 0.1	32.5 ± 0.1	32.3 ± 0.1*	32.1 ± 0.1**	31.6 ± 0.2**
Month 12	32.3 ± 0.2	32.1 ± 0.3	32.0 ± 0.2	31.6 ± 0.2*	31.5 ± 0.2*
Platelets (10^3/µL)					
Day 4	1,011.0 ± 16.0	1,063.0 ± 27.0	1,068.0 ± 22.0	1,203.0 ± 37.0**	1,172.0 ± 27.0**
Day 22	987.9 ± 32.9	993.3 ± 23.6	1,128.1 ± 58.9	1,847.4 ± 127.4**	3,537.1 ± 199.7**
Month 3	689.7 ± 18.8	714.4 ± 17.0	704.1 ± 15.9	706.8 ± 14.7	898.4 ± 64.9**
Month 6	644.7 ± 9.2	651.5 ± 13.2	649.3 ± 15.7	648.1 ± 22.2	663.8 ± 8.7
Month 12	575.1 ± 10.3	577.5 ± 8.2	579.1 ± 10.1	562.3 ± 21.4	587.1 ± 17.0
Platelet estimates					
Day 4	1,397.0 ± 84.0[b]	1,439.0 ± 56.0	1,512.0 ± 84.0	1,628.0 ± 80.0	1,401.0 ± 55.0
Day 22	1,199.0 ± 30.0	1,254.0 ± 47.0	1,268.0 ± 55.0	1,237.0 ± 48.0	1,359 ± 44.0
Month 3	949.2 ± 29.7	976.5 ± 31.0	1,010.1 ± 47.3	926.1 ± 22.2	984.9 ± 31.8
Month 6	707.7 ± 38.5	638.4 ± 24.9	688.8 ± 27.3	648.9 ± 25.5	636.3 ± 18.8
Month 12	1,138.2 ± 30.5	1,163.4 ± 29.1	1,089.9 ± 38.3	1,002.8 ± 73.6	999.6 ± 63.1
Leukocytes (10^3/µL)					
Day 4	9.23 ± 0.40	9.81 ± 0.42	7.94 ± 0.59	8.40 ± 0.46	9.88 ± 0.42
Day 22	10.85 ± 0.31	11.52 ± 0.33	10.29 ± 0.34	11.00 ± 0.48	11.45 ± 0.63
Month 3	11.52 ± 0.21	11.80 ± 0.21	10.88 ± 0.22	11.43 ± 0.23	12.96 ± 0.43*
Month 6	9.99 ± 0.27	9.81 ± 0.23	9.92 ± 0.27	9.19 ± 0.17	10.22 ± 0.27
Month 12	8.74 ± 0.17	8.76 ± 0.15	8.43 ± 0.19	8.45 ± 0.33	7.81 ± 0.12**
Segmented neutrophils (10^3/µL)					
Day 4	1.08 ± 0.05	1.09 ± 0.07	0.87 ± 0.04*	0.93 ± 0.03	0.98 ± 0.05
Day 22	0.98 ± 0.05	1.06 ± 0.06	0.92 ± 0.03	0.93 ± 0.05	1.05 ± 0.14
Month 3	1.36 ± 0.04	1.47 ± 0.06	1.44 ± 0.04	1.52 ± 0.04*	1.75 ± 0.10**
Month 6	1.54 ± 0.05	1.53 ± 0.05	1.57 ± 0.05	1.54 ± 0.05	1.68 ± 0.03
Month 12	2.22 ± 0.11	2.12 ± 0.07	1.80 ± 0.08**	1.82 ± 0.12*	1.77 ± 0.07**

TABLE E1
Hematology and Clinical Chemistry Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Hematology (continued)					
n					
Day 4	9	10	9	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	8	10
Lymphocytes (10^3/μL)					
Day 4	7.89 ± 0.37	8.43 ± 0.35	6.83 ± 0.56	7.26 ± 0.45	8.65 ± 0.38
Day 22	9.59 ± 0.27	10.10 ± 0.29	9.05 ± 0.31	9.76 ± 0.45	10.08 ± 0.49
Month 3	9.76 ± 0.19	9.90 ± 0.21	9.04 ± 0.18	9.52 ± 0.23	10.79 ± 0.36
Month 6	7.98 ± 0.24	7.82 ± 0.19	7.92 ± 0.25	7.24 ± 0.17	8.06 ± 0.24
Month 12	6.08 ± 0.14	6.21 ± 0.12	6.23 ± 0.13	6.21 ± 0.26	5.71 ± 0.11
Activated lymphocytes (10^3/μL)					
Day 4	0.06 ± 0.00	0.06 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.07 ± 0.01
Day 22	0.06 ± 0.01	0.07 ± 0.01	0.06 ± 0.01	0.08 ± 0.01	0.07 ± 0.01
Month 3	0.05 ± 0.00	0.06 ± 0.01	0.07 ± 0.00	0.05 ± 0.00	0.06 ± 0.00
Month 6	0.09 ± 0.00	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.10 ± 0.01
Month 12	0.05 ± 0.01	0.05 ± 0.00	0.04 ± 0.00	0.04 ± 0.01	0.04 ± 0.00
Monocytes (10^3/μL)					
Day 4	0.16 ± 0.01	0.17 ± 0.02	0.14 ± 0.02	0.13 ± 0.01	0.14 ± 0.01
Day 22	0.15 ± 0.01	0.22 ± 0.02*	0.19 ± 0.02	0.19 ± 0.01	0.20 ± 0.03
Month 3	0.22 ± 0.01	0.23 ± 0.01	0.19 ± 0.01	0.21 ± 0.01	0.23 ± 0.01
Month 6	0.24 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.21 ± 0.01	0.25 ± 0.01
Month 12	0.27 ± 0.03	0.24 ± 0.02	0.24 ± 0.01	0.25 ± 0.02	0.20 ± 0.01
Basophils (10^3/μL)					
Day 4	0.029 ± 0.002	0.031 ± 0.003	0.031 ± 0.004	0.029 ± 0.003	0.034 ± 0.003
Day 22	0.032 ± 0.003	0.040 ± 0.004	0.034 ± 0.003	0.027 ± 0.003	0.028 ± 0.003
Month 3	0.056 ± 0.004	0.060 ± 0.006	0.052 ± 0.004	0.054 ± 0.002	0.048 ± 0.003
Month 6	0.044 ± 0.004	0.043 ± 0.003	0.037 ± 0.003	0.035 ± 0.003	0.048 ± 0.010
Month 12	0.031 ± 0.004	0.038 ± 0.004	0.029 ± 0.004	0.021 ± 0.004	0.021 ± 0.002
Eosinophils (10^3/μL)					
Day 4	0.02 ± 0.00	0.03 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00
Day 22	0.04 ± 0.00	0.04 ± 0.00	0.03 ± 0.00*	0.02 ± 0.00**	0.02 ± 0.01**
Month 3	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.00	0.08 ± 0.01
Month 6	0.09 ± 0.01	0.08 ± 0.00	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.01
Month 12	0.09 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.10 ± 0.01	0.07 ± 0.01
Clinical Chemistry					
n					
Day 4	10	9	10	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	10	10
Urea nitrogen (mg/dL)					
Day 4	9.1 ± 0.3	9.4 ± 0.3	10.2 ± 0.4*	10.9 ± 0.4**	11.5 ± 0.3**
Day 22	15.6 ± 0.4	15.0 ± 0.5	15.6 ± 0.5	16.0 ± 0.3	16.6 ± 0.3
Month 3	17.8 ± 0.4	16.4 ± 0.6	18.2 ± 0.4	17.5 ± 0.3	17.5 ± 0.4
Month 6	15.7 ± 0.3	15.2 ± 0.4	15.4 ± 0.4	17.1 ± 0.4	15.8 ± 0.2
Month 12	16.1 ± 0.3	16.8 ± 0.3	16.8 ± 0.3	18.2 ± 0.6**	17.7 ± 0.3**

TABLE E1
Hematology and Clinical Chemistry Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Clinical Chemistry (continued)					
n					
Day 4	10	9	10	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	10	10
Creatinine (mg/dL)					
Day 4	0.41 ± 0.01	0.41 ± 0.02	0.44 ± 0.02	0.40 ± 0.00	0.41 ± 0.01
Day 22	0.52 ± 0.02	0.50 ± 0.02	0.52 ± 0.01	0.48 ± 0.02	0.47 ± 0.02
Month 3	0.70 ± 0.02	0.70 ± 0.02	0.69 ± 0.02	0.67 ± 0.02	0.66 ± 0.02
Month 6	0.70 ± 0.02	0.67 ± 0.02	0.62 ± 0.03**	0.65 ± 0.03*	0.62 ± 0.01**
Month 12	0.70 ± 0.03	0.74 ± 0.02	0.78 ± 0.02	0.66 ± 0.02	0.73 ± 0.03
Total protein (g/dL)					
Day 4	5.2 ± 0.1	5.3 ± 0.1	5.2 ± 0.2	5.0 ± 0.1	5.0 ± 0.1
Day 22	6.1 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	5.8 ± 0.1	5.7 ± 0.1*
Month 3	6.9 ± 0.1	6.9 ± 0.1	6.8 ± 0.1	6.7 ± 0.1	6.6 ± 0.1**
Month 6	6.5 ± 0.2	6.6 ± 0.0	6.6 ± 0.1	6.5 ± 0.1	6.3 ± 0.1*
Month 12	7.2 ± 0.1	7.2 ± 0.1	7.3 ± 0.1	7.0 ± 0.1	6.9 ± 0.1*
Albumin (g/dL)					
Day 4	3.7 ± 0.0	3.7 ± 0.1	3.7 ± 0.1	3.6 ± 0.0	3.6 ± 0.0
Day 22	4.2 ± 0.1	4.2 ± 0.0	4.1 ± 0.0	4.1 ± 0.0	4.1 ± 0.0
Month 3	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0
Month 6	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.3 ± 0.0**
Month 12	4.4 ± 0.0	4.5 ± 0.0	4.5 ± 0.0	4.4 ± 0.1	4.4 ± 0.0
Alanine aminotransferase (IU/L)					
Day 4	54 ± 2	53 ± 2	60 ± 3	68 ± 1**	70 ± 2**
Day 22	45 ± 1	46 ± 1	58 ± 2**	75 ± 3**	73 ± 4**
Month 3	82 ± 4	82 ± 12	135 ± 18*	176 ± 13**	216 ± 21**
Month 6	122 ± 15	114 ± 9	150 ± 12	238 ± 20**	210 ± 12**
Month 12	102 ± 6	107 ± 8	135 ± 10*	261 ± 23**	223 ± 15**
Alkaline phosphatase (IU/L)					
Day 4	639 ± 16	634 ± 22	592 ± 23	550 ± 11**	504 ± 9**
Day 22	542 ± 19	508 ± 15	498 ± 20	495 ± 19	471 ± 6**
Month 3	219 ± 3	204 ± 5*	195 ± 6**	168 ± 3**	182 ± 7**
Month 6	167 ± 3	160 ± 3	142 ± 5**	129 ± 3**	115 ± 2**
Month 12	146 ± 4	141 ± 3[c]	131 ± 8**	112 ± 6**	101 ± 2**
Creatine kinase (IU/L)					
Day 4	395 ± 39	405 ± 45	412 ± 15	431 ± 37	486 ± 43
Day 22	392 ± 65	319 ± 15	361 ± 31	334 ± 18	357 ± 42
Month 3	423 ± 41	388 ± 49	495 ± 65	531 ± 50	517 ± 54
Month 6	289 ± 35	293 ± 32	242 ± 14	367 ± 22	399 ± 14*
Month 12	176 ± 17	187 ± 18	184 ± 21	288 ± 28**	305 ± 20**
Sorbitol dehydrogenase (IU/L)					
Day 4	17 ± 1	15 ± 1	14 ± 1	15 ± 1	13 ± 1
Day 22	11 ± 1	10 ± 1	10 ± 1	9 ± 1	10 ± 1
Month 3	18 ± 3	20 ± 5	21 ± 4	28 ± 4	30 ± 4
Month 6	29 ± 2	27 ± 3	31 ± 2	49 ± 5**	36 ± 2*
Month 12	27 ± 1	27 ± 1	27 ± 1	31 ± 3	27 ± 0

TABLE E1
Hematology and Clinical Chemistry Data for Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
Clinical Chemistry (continued)					
n					
Day 4	10	9	10	10	10
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	10	10	10
Bile acids (μmol/L)					
Day 4	27.6 ± 2.9	26.9 ± 2.0	29.8 ± 2.1	31.6 ± 2.9	26.6 ± 1.3
Day 22	22.1 ± 1.9	24.5 ± 1.7	22.8 ± 1.5	24.7 ± 1.9	26.8 ± 1.4
Month 3	23.9 ± 3.2	24.0 ± 2.5	22.4 ± 2.2	27.7 ± 3.5	24.2 ± 2.2
Month 6	17.8 ± 1.7	25.5 ± 2.4*	18.7 ± 1.5	22.0 ± 1.7	20.0 ± 1.1
Month 12	29.2 ± 3.2	29.8 ± 4.7	26.8 ± 3.6	39.6 ± 4.2	27.4 ± 2.2

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=10
[c] n=9

TABLE E2
Hematology Data for Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	9	10	10
Hematocrit (auto) (%)					
Day 22	50.0 ± 0.7	49.2 ± 0.4	50.0 ± 0.9	50.6 ± 0.7	49.6 ± 0.5
Month 3	47.7 ± 0.7	49.9 ± 0.5*	49.2 ± 0.8	49.4 ± 0.6	50.4 ± 0.5*
Month 6	48.4 ± 0.7	49.2 ± 0.5	47.8 ± 0.6	48.0 ± 0.8	49.2 ± 0.8
Month 12	45.0 ± 0.5	45.6 ± 0.3	45.2 ± 0.6	45.0 ± 0.7	45.1 ± 0.8
Hematocrit (spun) (%)					
Day 22	50.0 ± 0.7	49.0 ± 0.3	49.4 ± 0.8	49.6 ± 0.7	48.5 ± 0.5
Month 3	48.3 ± 0.6	50.4 ± 0.5*	49.3 ± 0.6	49.4 ± 0.5	50.4 ± 0.4*
Month 6	49.0 ± 0.6	50.2 ± 0.5	48.7 ± 0.5	48.9 ± 0.8	49.9 ± 0.7
Month 12	46.5 ± 0.4	47.4 ± 0.2	46.9 ± 0.5	46.4 ± 0.6	46.7 ± 0.6
Hemoglobin (g/dL)					
Day 22	16.8 ± 0.2	16.5 ± 0.1	16.7 ± 0.3	16.9 ± 0.2	16.4 ± 0.2
Month 3	16.0 ± 0.2	16.7 ± 0.2*	16.4 ± 0.3	16.3 ± 0.2	16.5 ± 0.2
Month 6	16.1 ± 0.2	16.4 ± 0.2	16.0 ± 0.2	16.0 ± 0.3	16.2 ± 0.3
Month 12	14.9 ± 0.1	15.3 ± 0.2	15.1 ± 0.2	15.0 ± 0.2	14.9 ± 0.3
Erythrocytes (10^6/µL)					
Day 22	10.25 ± 0.15	10.20 ± 0.08	10.47 ± 0.19	10.77 ± 0.13*	10.61 ± 0.13*
Month 3	10.10 ± 0.16	10.66 ± 0.13*	10.55 ± 0.17*	10.95 ± 0.10**	11.55 ± 0.16**
Month 6	10.56 ± 0.15	10.81 ± 0.10	10.60 ± 0.13	10.77 ± 0.20	11.50 ± 0.20**
Month 12	9.58 ± 0.10	9.72 ± 0.09	9.77 ± 0.10	9.95 ± 0.13*	10.30 ± 0.21**
Reticulocytes (auto) (10^6/µL)					
Day 22	0.32 ± 0.01	0.30 ± 0.01	0.33 ± 0.02	0.31 ± 0.01	0.32 ± 0.02
Month 3	0.33 ± 0.01	0.31 ± 0.01	0.34 ± 0.02	0.34 ± 0.03	0.34 ± 0.02
Month 6	0.36 ± 0.02	0.37 ± 0.01	0.39 ± 0.04	0.36 ± 0.03	0.35 ± 0.02
Month 12	0.32 ± 0.02	0.33 ± 0.01	0.32 ± 0.01	0.36 ± 0.02	0.37 ± 0.02
Reticulocytes (manual) (10^6/µL)					
Day 22	0.21 ± 0.04	0.12 ± 0.02	0.16 ± 0.02	0.11 ± 0.01*	0.14 ± 0.02
Month 3	0.25 ± 0.02[b]	0.19 ± 0.03	0.21 ± 0.03[c]	0.24 ± 0.02	0.23 ± 0.02
Nucleated erythrocytes (10^3/µL)					
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 3	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 6	0.10 ± 0.10	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Month 12	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[c]
Mean cell volume (fL)					
Day 22	48.8 ± 0.2	48.3 ± 0.1*	47.8 ± 0.2**	47.0 ± 0.2**	46.8 ± 0.2**
Month 3	47.2 ± 0.1	46.9 ± 0.3	46.7 ± 0.1	45.1 ± 0.2**	43.7 ± 0.3**
Month 6	45.8 ± 0.2	45.5 ± 0.3	45.1 ± 0.2*	44.6 ± 0.2**	42.8 ± 0.3**
Month 12	46.9 ± 0.3	46.9 ± 0.3	46.3 ± 0.3	45.2 ± 0.2**	43.9 ± 0.5**
Mean cell hemoglobin (pg)					
Day 22	16.4 ± 0.1	16.2 ± 0.0*	15.9 ± 0.1**	15.7 ± 0.1**	15.5 ± 0.1**
Month 3	15.8 ± 0.0	15.7 ± 0.1	15.6 ± 0.0**	14.9 ± 0.1**	14.3 ± 0.1**
Month 6	15.3 ± 0.1	15.2 ± 0.1	15.1 ± 0.1	14.9 ± 0.1**	14.1 ± 0.1**
Month 12	15.5 ± 0.1	15.7 ± 0.2	15.5 ± 0.1	15.1 ± 0.1*	14.4 ± 0.2**

TABLE E2
Hematology Data for Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	9	10	10
Mean cell hemoglobin concentration (g/dL)					
Day 22	33.6 ± 0.1	33.5 ± 0.1	33.3 ± 0.2	33.4 ± 0.1	33.1 ± 0.1**
Month 3	33.5 ± 0.1	33.5 ± 0.1	33.3 ± 0.1	33.1 ± 0.1**	32.8 ± 0.1**
Month 6	33.4 ± 0.2	33.4 ± 0.1	33.5 ± 0.2	33.4 ± 0.1	32.9 ± 0.1
Month 12	33.1 ± 0.2	33.5 ± 0.2	33.4 ± 0.1	33.3 ± 0.1	32.9 ± 0.1
Platelets (10^3/μL)					
Day 22	905.7 ± 48.4	939.2 ± 36.5	933.3 ± 47.4	851.4 ± 54.9	963.9 ± 48.0
Month 3	890.7 ± 37.4	839.5 ± 63.4	837.2 ± 57.0	888.2 ± 73.9	720.0 ± 47.1
Month 6	972.9 ± 62.5	819.3 ± 55.4	928.9 ± 91.0	923.1 ± 55.7	921.4 ± 62.9
Month 12	1,078.1 ± 67.6	925.0 ± 37.9	932.6 ± 78.1	879.9 ± 46.7*	761.5 ± 34.4**
Platelet estimates (10^3/μL)					
Day 22	1,630.0 ± 105.0	1,903.0 ± 83.0	1,462.0 ± 91.0	1,319.0 ± 61.0	1,825.0 ± 105.0
Month 3	1,296.0 ± 92.0	1,208.0 ± 104.0	1,166.0 ± 81.0	1,342.0 ± 98.0	1,126.0 ± 90.0
Month 6	1,073.1 ± 52.7	998.0 ± 71.8	890.4 ± 74.0	978.6 ± 55.8	940.8 ± 39.5
Month 12	968.3 ± 61.6[c]	932.4 ± 57.4	987.0 ± 90.4	915.6 ± 44.8	828.3 ± 44.2[c]
Leukocytes (10^3/μL)					
Day 22	5.10 ± 0.51	6.58 ± 0.35*	7.19 ± 0.49**	7.26 ± 0.57*	7.89 ± 0.39**
Month 3	4.46 ± 0.24	4.48 ± 0.33	5.05 ± 0.30	5.32 ± 0.36	4.74 ± 0.48
Month 6	6.49 ± 0.42	5.69 ± 0.22	6.25 ± 0.51	6.62 ± 0.54	5.30 ± 0.33
Month 12	5.86 ± 0.51	4.84 ± 0.28	5.64 ± 0.35	5.67 ± 0.53	5.12 ± 0.40
Segmented neutrophils (10^3/μL)					
Day 22	0.48 ± 0.06	0.60 ± 0.03	0.63 ± 0.06	0.75 ± 0.11*	0.83 ± 0.07**
Month 3	0.53 ± 0.04	0.47 ± 0.07	0.60 ± 0.05	0.66 ± 0.05	0.53 ± 0.05
Month 6	0.85 ± 0.08	0.72 ± 0.04	0.80 ± 0.08	0.89 ± 0.07	0.75 ± 0.10
Month 12	1.06 ± 0.11	0.88 ± 0.08	1.03 ± 0.06	0.93 ± 0.07	0.73 ± 0.05**
Lymphocytes (10^3/μL)					
Day 22	4.36 ± 0.44	5.66 ± 0.32*	6.22 ± 0.41**	6.17 ± 0.46**	6.61 ± 0.33**
Month 3	3.67 ± 0.21	3.68 ± 0.24	4.09 ± 0.28	4.32 ± 0.32	3.85 ± 0.43
Month 6	5.17 ± 0.34	4.61 ± 0.17	4.96 ± 0.42	5.22 ± 0.44	4.14 ± 0.23
Month 12	4.42 ± 0.40	3.62 ± 0.22	4.14 ± 0.33	4.30 ± 0.45	4.05 ± 0.32
Activated lymphocytes (10^3/μL)					
Day 22	0.02 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	0.03 ± 0.00	0.04 ± 0.00**
Month 3	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00	0.02 ± 0.00
Month 6	0.03 ± 0.01	0.03 ± 0.00	0.04 ± 0.01	0.04 ± 0.01	0.02 ± 0.00
Month 12	0.03 ± 0.01	0.02 ± 0.00	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.00*
Monocytes (10^3/μL)					
Day 22	0.08 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.12 ± 0.01*	0.16 ± 0.01**
Month 3	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.00	0.09 ± 0.01
Month 6	0.22 ± 0.02	0.16 ± 0.02	0.18 ± 0.02	0.22 ± 0.02	0.16 ± 0.02
Month 12	0.22 ± 0.02	0.19 ± 0.02	0.25 ± 0.02	0.23 ± 0.03	0.17 ± 0.02
Basophils (10^3/μL)					
Day 22	0.014 ± 0.003	0.017 ± 0.002	0.023 ± 0.003	0.019 ± 0.002	0.031 ± 0.005**
Month 3	0.024 ± 0.004	0.022 ± 0.003	0.023 ± 0.004	0.022 ± 0.004	0.024 ± 0.003
Month 6	0.015 ± 0.002	0.015 ± 0.003	0.035 ± 0.009	0.021 ± 0.006	0.016 ± 0.003
Month 12	0.016 ± 0.003	0.016 ± 0.003	0.028 ± 0.007	0.031 ± 0.007	0.020 ± 0.003

TABLE E2
Hematology Data for Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n					
Day 22	10	10	10	10	10
Month 3	10	10	10	10	10
Month 6	10	10	10	10	10
Month 12	10	10	9	10	10
Eosinophils (10^3/μL)					
Day 22	0.15 ± 0.02	0.18 ± 0.02	0.18 ± 0.02	0.18 ± 0.02	0.22 ± 0.03
Month 3	0.12 ± 0.02	0.21 ± 0.04	0.23 ± 0.04*	0.21 ± 0.02*	0.23 ± 0.03**
Month 6	0.20 ± 0.05	0.16 ± 0.03	0.23 ± 0.04	0.23 ± 0.05	0.21 ± 0.04
Month 12	0.12 ± 0.02	0.11 ± 0.02	0.16 ± 0.03	0.16 ± 0.02	0.13 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=8
[c] n=9

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF SODIUM DICHROMATE DIHYDRATE

Sodium dichromate dihydrate was obtained from Aldrich Chemical Company (Milwaukee, WI) in two lots (15301BI and 13822LI). The two lots were combined at the analytical chemistry laboratory, Battelle Memorial Institute (Columbus, OH), and assigned a new lot number (062001). Lot 062001 was used in the 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, the study laboratory (Southern Research Institute, Birmingham, AL), Galbraith Laboratories, Inc. (Knoxville, TN), and Elemental Analysis Corp. (Lexington, KY). Reports on analyses performed in support of the sodium dichromate dihydrate studies are on file at the National Institute of Environmental Health Sciences.

Lot 062001, an orange crystalline solid, was identified as sodium dichromate dihydrate by the analytical chemistry laboratory using X-ray diffraction (XRD), by the analytical chemistry laboratory and by Galbraith Laboratories, Inc., using elemental analysis by inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and by Elemental Analysis Corp. using proton-induced X-ray emission spectroscopy (PIXE). The XRD powder patterns were consistent with a reference pattern (International Centre for Diffraction Data, 2000); XRD diffractograms are presented in Figure F1. Elemental analyses for chromium and sodium by ICP-AES were in agreement with the theoretical values for sodium dichromate dihydrate, and PIXE indicated the absence of significant metallic impurities. A PIXE spectrum is presented in Figure F2.

The moisture content of lot 062001 was determined by Galbraith Laboratories, Inc., using Karl Fischer titration. The purity of lot 062001 was determined by the analytical chemistry laboratory using differential scanning calorimetry (DSC), titration of the dichromate ion with sodium thiosulfate and potassium ferrocyanide, and speciation of the chromium ions using liquid chromatography-inductively coupled plasma-mass spectrometry (LC-ICP-MS) and by the study laboratory using potentiometric titration with sodium thiosulfate. DSC was performed using a Perkin-Elmer DSC-7 scanning calorimeter from 342° to 365° C with a temperature increase of 1° C per minute under a nitrogen atmosphere. Titration with sodium thiosulfate was performed by titrating a solution of sodium dichromate dihydrate and potassium iodide in dilute hydrochloric acid with 0.1 N sodium thiosulfate using a double sheet platinum electrode and a Brinkman Metrohm titrator or its equivalent. Titration with potassium ferrocyanide was performed by titrating a solution of sodium dichromate dihydrate with 0.1 N potassium ferrocyanide trihydrate as previously described. LC-ICP-MS was conducted using system A.

A) Hewlett-Packard (Palo Alto, CA) 1100 series high performance liquid chromatography system, a Dionex Corp. (Sunnyvale, CA) IonPac® AS7 ion exchange column (250 mm × 4 mm), with an isocratic mobile phase of 35 mM ammonium sulfate adjusted to pH 9.2 with ammonium hydroxide at a flow rate of 1 mL/minute and ICP-MS detection

Karl Fischer titration indicated a water content of 11.62%, which is in agreement with the theoretical value of 12.09%. DSC indicated a purity of 99.73% ± 0.15%. Titration with sodium thiosulfate by the analytical chemistry laboratory indicated a purity of 99.7% ± 0.1%. Titration with sodium thiosulfate by the study laboratory indicated purities of 101% and 102% relative to a frozen reference standard of the same lot. Titration with potassium ferrocyanide indicated a purity of 103.1% ± 0.2%. LC-ICP-MS indicated that the concentration of Cr III, if present, was less than 0.1%. Representative LC-ICP-MS spectra are presented in Figure F3. The overall purity of lot 062001 was determined to be greater than 99.7%.

To ensure stability, the bulk chemical was stored at room temperature, protected from light in amber glass bottles. Periodic reanalyses of the bulk chemical were performed by the study laboratory using potentiometric titration as described for the purity assays; no degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared approximately every 2 weeks by mixing sodium dichromate dihydrate with tap water (Table F1). Formulations were stored in NALGENE® containers at room temperature for up to 42 days.

Because all dose formulations in these studies were determined to be solutions, no homogeneity studies were required. Stability studies of a 41.8 µg/mL dose formulation were performed by the analytical chemistry laboratory using ion chromatography by system B. Stability was confirmed for at least 42 days for dose formulations stored in sealed NALGENE® containers, protected from light, at temperatures up to room temperature and for at least 7 days when stored in drinking water bottles under simulated animal room conditions.

B) Dionex Corp. IonPac® AS7 ion exchange column (250 mm × 4 mm), using an isocratic mobile phase of 250 mM ammonium sulfate and 100 mM ammonium hydroxide at a flow rate of 1 mL/minute, with postcolumn derivitization using 2 mM 1,5-diphenylcarbazide in methanol:water:concentrated sulfuric acid (100:872:28) at a flow rate of 0.5 mL/minute and visible light (520 nm) detection

Periodic analyses of the dose formulations of sodium dichromate dihydrate were conducted by the study laboratory using ultraviolet/visible/near infrared spectroscopy (350 to 390 nm). The dose formulations were analyzed approximately every 10 weeks (Table F2). Of the dose formulations analyzed, all 44 for rats and all 84 for mice were within 10% of the target concentrations. Animal room samples and unused carboy storage samples of these dose formulations were also analyzed; all 16 animal room samples for rats and 34 of 35 animal room samples for mice were within 10% of the target concentrations. Fourteen of 16 carboy samples for rats and 33 of 35 carboy samples for mice were within 10% of the target concentrations.

The sodium dichromate dihydrate dosed water used in these studies was slightly acidic. Based on an equilibrium constant of 50, dichromate predominates at the highest exposure concentration and the chromate:dichromate ratio approaches 1 at the lowest exposure concentration.

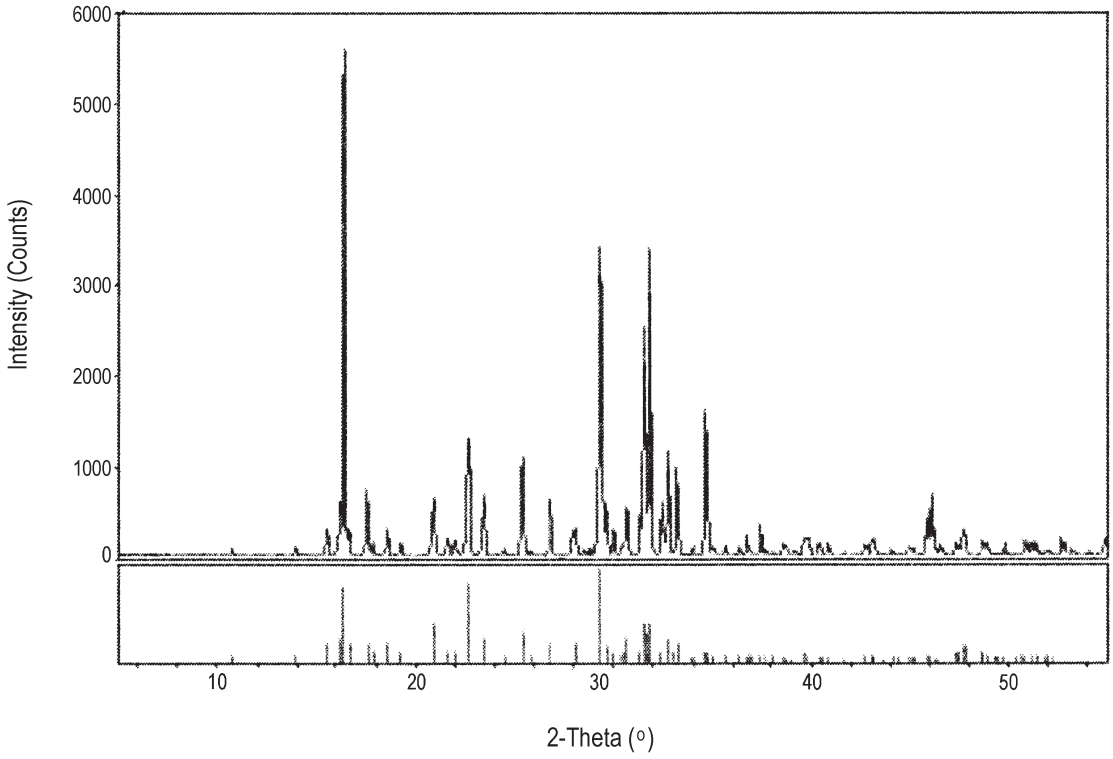

FIGURE F1
X-Ray Diffraction Diffractograms of Sodium Dichromate Dihydrate
Upper plot: lot 062001. Lower plot: reference sample

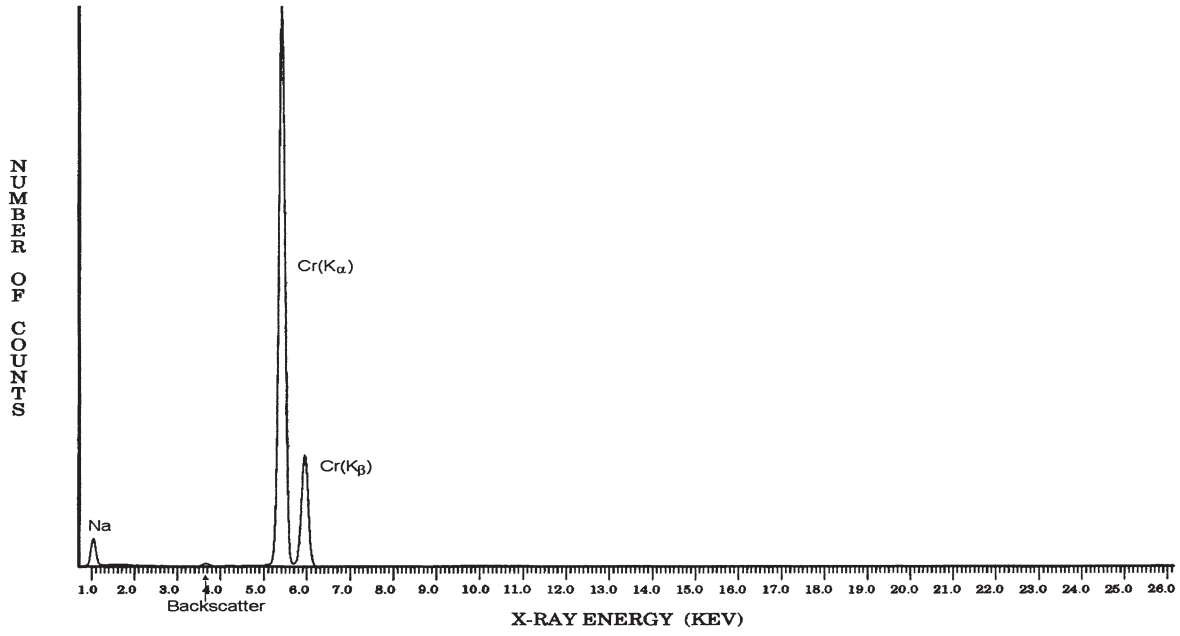

FIGURE F2
Proton-Induced X-Ray Emission Spectrum of Sodium Dichromate Dihydrate

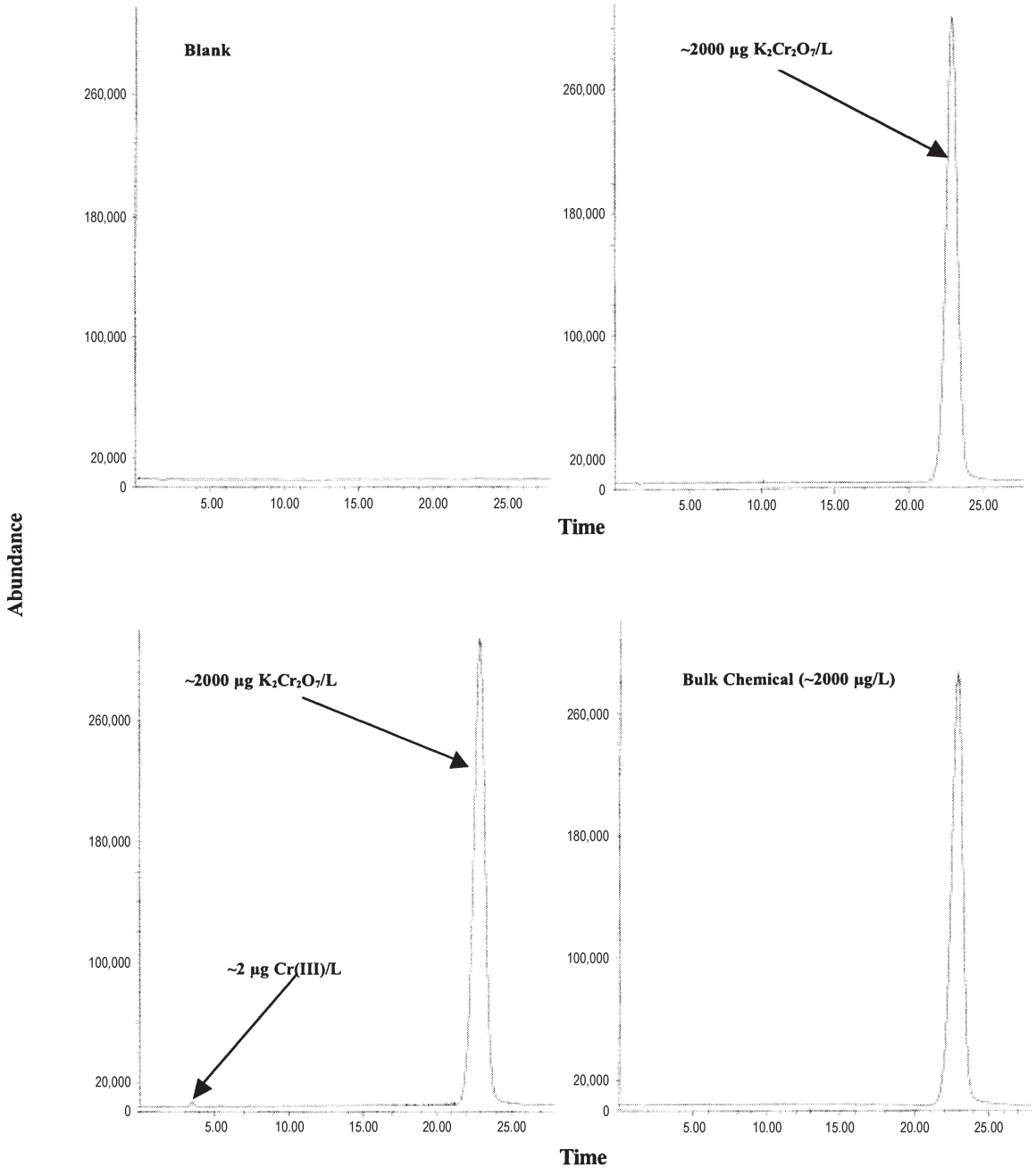

FIGURE F3
Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometry
Selected Ion-Current Profiles of Cr III and Cr VI in Sodium Dichromate Dihydrate

TABLE F1
Preparation and Storage of Dose Formulations in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Preparation
A premix was prepared in a beaker with tap water and then thoroughly mixed with additional tap water in a mixing tank. The dose formulations were prepared approximately every 2 weeks.

Chemical Lot Number
062001

Maximum Storage Time
42 days

Storage Conditions
Stored in NALGENE® containers at room temperature and protected from light

Study Laboratory
Southern Research Institute (Birmingham, AL)

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Rats				
September 18, 2002	September 19, 2002	14.3	14.0	–2
		57.3	59.8	+4
		172	172	0
		516	517	0
	October 16, 2002[b]	14.3	14.0	–2
		57.3	60.8	+6
		172	177	+3
		516	529	+3
	October 16, 2002[c]	14.3	14.7	+3
		57.3	61.7	+8
		172	179	+4
		516	531	+3
November 27, 2002	December 2, 2002	14.3	14.4	+1
		57.3	59.5	+4
		172	175	+2
		516	521	+1
February 5, 2003	February 6 and 10, 2003	14.3	15.3	+7
		57.3	60.3	+5
		172	189	+10
		516	523	+1
April 18, 2003	April 21, 2003	14.3	14.6	+2
		57.3	59.7	+4
		172	174	+1
		516	526	+2
	May 14, 2003[b]	14.3	13.3	–7
		57.3	59.7	+4
		172	177	+3
		516	522	+1
	May 14, 2003[c]	14.3	15.0	+5
		57.3	62.0	+8
		172	191	+11
		516	520	+1
June 27, 2003	June 30, 2003	14.3	15.0	+5
		57.3	59.4	+4
		172	175	+2
		516	519	+1
September 5, 2003	September 8, 2003	14.3	14.8	+3
		57.3	59.8	+4
		172	175	+2
		516	520	+1

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration (mg/L)	Difference from Target (%)
Rats (continued)				
November 14, 2003	November 17, 2003	14.3	14.0	–2
		57.3	58.0	+1
		172	171	–1
		516	515	0
	December 10, 2003[b]	14.3	14.4	+1
		57.3	57.5	0
		172	175	+2
		516	513	–1
	December 10, 2003[c]	14.3	14.8	+3
		57.3	57.6	+1
		172	173	+1
		516	523	+1
January 23, 2004	January 26, 2004	14.3	15.6	+9
		57.3	59.2	+3
		172	173	+1
		516	515	0
April 2, 2004	April 5, 2004	14.3	15.3	+7
		57.3	59.6	+4
		172	175	+2
		516	521	+1
June 11, 2004	June 14, 2004	14.3	14.2	–1
		57.3	59.7	+4
		172	177	+3
		516	529	+3
	July 8, 2004[b]	14.3	14.6	+2
		57.3	63.1	+10
		172	185	+8
		516	546	+6
	July 8, 2004[c]	14.3	14.9	+4
		57.3	65.6	+14
		172	186	+8
		516	550	+7
August 20, 2004	August 23, 2004	14.3	14.4	+1
		57.3	58.9	+3
		172	176	+2
		516	526	+2

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration (mg/L)	Difference from Target (%)
Mice				
August 20, 2002	August 22, 2002	14.3	14.4	+1
		28.6	29.3	+2
		57.3	57.3	0
		85.7	87.9	+3
		172	169	–2
		257.4	261	+1
		516	517	0
	September 19, 2002[b]	14.3	14.4	+1
		28.6	29.0	+1
		57.3	57.5	0
		85.7	87.1	+2
		172	132	–23
		257.4	265	+3
		516	515	0
	September 19, 2002[c]	14.3	14.3	0
		28.6	29.1	+2
		57.3	57.6	+1
		85.7	87.3	+2
		172	169	–2
		257.4	265	+3
		516	517	0
September 18, 2002	September 19, 2002	14.3	14.0	–2
		28.6	28.1	–2
		57.3	59.8	+4
		85.7	85.0	–1
		172	172	0
		257.4	254	–1
		516	517	0
	October 16, 2002[b]	14.3	14.7	+3
		28.6	29.2	+2
		57.3	61.4	+7
		85.7	88.6	+3
		172	177	+3
		257.4	264	+3
		516	524	+2
	October 16, 2002[c]	14.3	14.7	+3
		28.6	29.7	+4
		57.3	61.7	+8
		85.7	89.1	+4
		172	179	+4
		257.4	264	+3
		516	531	+3

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration (mg/L)	Difference from Target (%)
Mice (continued)				
November 27, 2002	December 2, 2002	14.3	14.4	+1
		28.6	29.8	+4
		57.3	59.5	+4
		85.7	88.7	+4
		172	175	+2
		257.4	266	+3
		516	521	+1
February 5, 2003	February 6 and 10, 2003	14.3	15.3	+7
		28.6	29.2	+2
		57.3	60.3	+5
		85.7	91.1	+6
		172	189	+10
		257.4	268	+4
		516	523	+1
April 18, 2003	April 21, 2003	14.3	14.6	+2
		28.6	29.3	+2
		57.3	59.7	+4
		85.7	85.9	0
		172	174	+1
		257.4	258	0
		516	526	+2
	May 14, 2003[b]	14.3	13.7	–4
		28.6	29.4	+3
		57.3	58.8	+3
		85.7	88.6	+3
		172	177	+3
		257.4	259	+1
		516	518	0
	May 14, 2003[c]	14.3	15.0	+5
		28.6	30.1	+5
		57.3	62.0	+8
		85.7	89.2	+4
		172	191	+11
		257.4	262	+2
		516	520	+1
June 27, 2003	June 30, 2003	14.3	15.0	+5
		28.6	28.8	+1
		57.3	59.4	+4
		85.7	88.2	+3
		172	175	+2
		257.4	250	–3
		516	519	+1

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration (mg/L)	Difference from Target (%)
Mice (continued)				
September 5, 2003	September 8, 2003	14.3	14.8	+3
		28.6	28.5	0
		57.3	59.8	+4
		85.7	86.0	0
		172	175	+2
		257.4	258	0
		516	520	+1
November 14, 2003	November 17, 2003	14.3	14.0	–2
		28.6	28.8	+1
		57.3	58.0	+1
		85.7	82.9	–3
		172	171	–1
		257.4	255	–1
		516	515	0
	December 10, 2003[b]	14.3	14.7	+3
		28.6	29.5	+3
		57.3	57.7	+1
		85.7	85.8	0
		172	177	+3
		257.4	256	–1
		516	511	–1
	December 10, 2003[c]	14.3	14.8	+3
		28.6	29.5	+3
		57.3	57.6	+1
		85.7	85.4	0
		172	173	+1
		257.4	253	–2
		516	523	+1
January 23, 2004	January 26, 2004	14.3	15.6	+9
		28.6	30.0	+5
		57.3	59.2	+3
		85.7	90.9	+6
		172	173	+1
		257.4	257	0
		516	515	0
April 2, 2004	April 5, 2004	14.3	15.3	+7
		28.6	28.9	+1
		57.3	59.6	+4
		85.7	87.9	+3
		172	175	+2
		257.4	256	–1
		516	521	+1

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration (mg/L)	Difference from Target (%)
Mice (continued)				
June 11, 2004	June 14, 2004	14.3	14.2	–1
		28.6	28.9	+1
		57.3	59.7	+4
		85.7	85.8	0
		172	177	+3
		257.4	261	+1
		516	529	+3
	July 8, 2004[b]	14.3	14.6	+2
		28.6	30.8	+8
		57.3	62.8	+10
		85.7	92.2	+8
		172	185	+8
		257.4	277	+8
		516	546	+6
	July 8, 2004[c]	14.3	14.9	+4
		28.6	31.0	+8
		57.3	65.6	+14
		85.7	91.9	+7
		172	186	+8
		257.4	275	+7
		516	550	+7
August 20, 2004	August 23, 2004	14.3	14.4	+1
		28.6	28.9	+1
		57.3	58.9	+3
		85.7	85.8	0
		172	176	+2
		257.4	254	–1
		516	526	+2

[a] Results of duplicate analyses
[b] Animal room samples from drinking water bottles
[c] Unused samples from carboy storage containers

APPENDIX G
WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF SODIUM DICHROMATE DIHYDRATE

TABLE G1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	16.7	118	16.6	117	2.0	16.0	117	7.9
2	17.1	151	17.2	149	1.7	16.9	146	6.6
3	19.5	185	19.3	183	1.5	19.0	181	6.0
4	19.4	218	19.0	215	1.3	19.3	213	5.2
5	18.7	243	18.7	240	1.1	18.5	239	4.4
6	18.4	261	17.8	257	1.0	17.8	257	4.0
7	18.0	275	17.7	271	0.9	17.3	272	3.6
8	18.1	289	18.1	286	0.9	17.2	285	3.5
9	18.0	305	18.2	301	0.9	17.3	302	3.3
10	18.0	317	18.0	312	0.8	17.3	313	3.2
11	17.6	334	17.4	329	0.8	16.7	331	2.9
12	17.7	345	17.1	340	0.7	17.0	339	2.9
13	17.3	351	17.7	345	0.7	17.2	348	2.8
17	16.2	387	16.2	381	0.6	15.9	383	2.4
21	16.7	410	16.5	404	0.6	16.3	407	2.3
25	16.6	434	16.1	427	0.5	15.9	431	2.1
29	17.2	451	17.0	443	0.5	16.7	448	2.1
33	17.4	468	17.3	458	0.5	17.1	464	2.1
37	16.8	480	16.2	471	0.5	16.1	477	1.9
41	14.8	488	14.6	478	0.4	14.8	483	1.8
45	15.6	490	15.4	485	0.5	16.4	488	1.9
49	16.0	501	16.1	493	0.5	16.5	497	1.9
53	16.4	511	17.1	502	0.5	16.9	505	1.9
57	17.3	515	17.2	507	0.5	17.4	512	1.9
61	16.7	523	16.9	515	0.5	17.1	519	1.9
65	16.5	524	16.1	515	0.4	16.7	519	1.8
69	15.7	525	16.1	516	0.4	16.0	518	1.8
73	15.7	525	15.7	517	0.4	16.1	520	1.8
77	17.0	530	16.2	519	0.4	16.6	525	1.8
81	16.3	532	16.4	518	0.5	16.1	525	1.8
85	15.9	531	16.1	515	0.4	16.0	522	1.8
89	16.2	527	16.4	518	0.5	15.6	518	1.7
93	17.4	526	18.2	517	0.5	18.7	520	2.1
97	15.7	513	16.5	515	0.5	15.9	517	1.8
101	18.1	515	16.2	503	0.5	16.7	514	1.9
Mean for weeks								
1-13	18.0	261	17.9	257	1.1	17.5	257	4.3
14-52	16.4	457	16.2	449	0.5	16.2	453	2.1
53-101	16.5	523	16.5	514	0.5	16.6	518	1.8

TABLE G1
Water and Compound Consumption by Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	172 mg/L			516 mg/L		
	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	14.4	117	21.2	12.6	118	55.2
2	15.0	147	17.5	13.2	143	47.8
3	16.8	180	16.1	14.9	173	44.4
4	16.6	210	13.6	14.8	201	37.9
5	16.3	235	11.9	14.7	225	33.7
6	15.5	254	10.5	14.2	243	30.2
7	14.8	267	9.5	13.8	257	27.7
8	14.5	279	8.9	13.8	270	26.4
9	14.5	295	8.5	14.7	285	26.6
10	14.5	304	8.2	13.4	295	23.4
11	14.4	321	7.7	13.1	311	21.8
12	13.9	330	7.2	12.7	320	20.5
13	14.1	338	7.2	14.5	324	23.1
17	13.4	373	6.2	13.0	363	18.5
21	14.1	395	6.1	13.3	386	17.8
25	14.4	418	5.9	13.5	407	17.1
29	14.7	437	5.8	14.0	424	17.0
33	14.9	449	5.7	13.9	437	16.4
37	14.0	462	5.2	13.6	447	15.7
41	13.2	469	4.8	12.2	454	13.9
45	14.0	477	5.0	13.2	461	14.8
49	13.8	486	4.9	12.8	468	14.1
53	14.9	490	5.2	14.0	475	15.2
57	14.7	496	5.1	13.8	479	14.9
61	14.5	503	5.0	13.4	485	14.3
65	14.1	504	4.8	13.4	484	14.3
69	14.0	503	4.8	12.9	484	13.8
73	13.8	501	4.7	12.7	483	13.6
77	13.7	508	4.6	12.5	487	13.3
81	13.4	507	4.5	12.3	483	13.2
85	13.5	506	4.6	12.3	473	13.4
89	13.1	502	4.5	12.3	478	13.3
93	14.1	500	4.9	13.4	474	14.6
97	14.1	500	4.9	11.7	459	13.2
101	14.1	500	4.9	12.0	455	13.6
Mean for weeks						
1-13	15.0	252	11.4	13.9	243	32.2
14-52	14.1	441	5.5	13.3	427	16.1
53-101	14.0	502	4.8	12.8	477	13.9

[a] Grams of drinking water consumed per animal per day
[b] Milligrams of sodium dichromate dihydrate consumed per kilogram body weight per day

TABLE G2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	13.5	100	13.3	99	1.9	13.5	100	7.8
2	13.3	122	13.0	120	1.6	12.8	121	6.1
3	14.2	135	13.7	132	1.5	13.6	134	5.8
4	13.7	150	13.2	146	1.3	13.1	147	5.1
5	13.5	157	13.3	154	1.2	12.6	154	4.7
6	12.9	164	13.1	161	1.2	12.5	162	4.4
7	12.8	170	12.9	168	1.1	12.1	167	4.1
8	13.0	175	13.0	172	1.1	12.0	172	4.0
9	12.8	180	12.6	178	1.0	12.4	177	4.0
10	12.8	183	12.4	180	1.0	11.7	180	3.7
11	12.7	188	12.3	184	1.0	12.1	185	3.8
12	13.0	193	12.5	189	0.9	11.4	188	3.5
13	12.3	198	11.5	193	0.9	10.9	192	3.2
17	12.1	208	11.4	203	0.8	10.7	202	3.0
21	12.2	217	11.9	211	0.8	11.2	209	3.1
25	11.6	229	11.6	223	0.7	11.2	221	2.9
29	12.1	237	11.6	229	0.7	11.8	229	2.9
33	12.8	246	12.9	239	0.8	12.3	237	3.0
37	12.3	255	12.0	248	0.7	11.7	246	2.7
41	10.8	263	10.7	255	0.6	10.6	253	2.4
45	12.1	272	11.8	261	0.6	11.6	262	2.5
49	12.3	281	11.8	271	0.6	11.1	271	2.3
53	12.1	289	12.1	279	0.6	11.5	278	2.4
57	12.6	297	12.6	288	0.6	12.2	287	2.4
61	12.6	309	12.2	297	0.6	11.8	297	2.3
65	12.4	314	12.2	302	0.6	12.2	304	2.3
69	12.5	317	11.9	307	0.6	11.9	310	2.2
73	12.4	323	12.5	312	0.6	11.6	315	2.1
77	13.4	332	12.3	323	0.5	11.4	320	2.0
81	12.8	337	12.0	328	0.5	12.0	325	2.1
85	12.5	341	12.5	332	0.5	11.8	333	2.0
89	13.4	334	11.9	333	0.5	12.6	333	2.2
93	15.1	348	13.3	333	0.6	12.6	340	2.1
97	13.9	350	13.7	339	0.6	12.9	346	2.1
101	15.0	351	14.4	338	0.6	12.7	346	2.1
Mean for weeks								
1-13	13.1	163	12.8	160	1.2	12.4	160	4.6
14-52	12.0	245	11.7	238	0.7	11.4	237	2.8
53-101	13.1	326	12.6	316	0.6	12.1	318	2.2

TABLE G2
Water and Compound Consumption by Female Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	172 mg/L			516 mg/L		
	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	10.7	99	18.5	9.6	99	50.2
2	10.9	119	15.8	9.4	115	42.3
3	11.2	131	14.7	10.5	129	42.1
4	11.0	145	13.1	10.0	144	35.9
5	10.8	153	12.2	10.0	152	33.9
6	11.3	161	12.1	9.4	159	30.5
7	10.4	166	10.8	9.5	165	29.7
8	10.0	171	10.1	9.3	170	28.3
9	10.0	175	9.8	9.5	175	28.1
10	10.0	178	9.7	9.2	178	26.7
11	10.0	183	9.4	8.8	182	25.0
12	9.8	186	9.0	8.9	186	24.8
13	9.6	192	8.6	8.4	190	22.8
17	9.6	201	8.2	9.0	199	23.3
21	9.9	206	8.3	9.0	207	22.4
25	9.8	218	7.7	8.9	215	21.3
29	9.7	226	7.4	9.1	222	21.1
33	11.0	235	8.1	9.3	230	20.9
37	10.2	242	7.2	9.2	237	20.1
41	9.5	248	6.6	8.6	242	18.3
45	10.3	256	6.9	9.1	248	19.0
49	10.3	265	6.7	9.3	254	18.9
53	10.7	272	6.8	9.4	263	18.4
57	11.1	279	6.9	9.8	268	18.8
61	11.1	290	6.6	9.4	275	17.7
65	10.6	296	6.2	9.4	281	17.3
69	10.6	302	6.0	9.4	284	17.1
73	11.0	308	6.1	9.5	287	17.1
77	12.1	318	6.5	9.6	298	16.6
81	10.4	319	5.6	8.8	300	15.2
85	10.6	323	5.7	9.9	307	16.6
89	11.0	324	5.8	9.8	314	16.1
93	11.5	328	6.0	10.0	315	16.4
97	11.6	337	5.9	9.7	318	15.7
101	11.5	340	5.8	9.8	312	16.2
Mean for weeks						
1-13	10.4	158	11.8	9.4	157	32.3
14-52	10.0	233	7.5	9.1	228	20.6
53-101	11.1	310	6.1	9.6	294	16.9

[a] Grams of drinking water consumed per animal per day
[b] Milligrams of sodium dichromate dihydrate consumed per kilogram body weight per day

TABLE G3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	0 mg/L		14.3 mg/L			28.6 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	3.9	23.2	4.0	23.2	3	4.3	23.5	5
2	4.0	25.3	3.9	25.3	2	4.0	25.7	5
3	3.8	26.8	3.9	26.9	2	3.8	27.1	4
4	3.8	28.0	3.7	28.2	2	3.9	28.5	4
5	3.9	29.9	4.0	30.0	2	3.8	30.3	4
6	3.7	31.5	3.7	31.5	2	3.8	31.9	3
7	3.7	32.9	3.8	33.0	2	3.7	33.4	3
8	3.6	34.2	3.6	34.5	2	3.6	34.8	3
9	3.5	35.9	3.5	36.3	1	3.6	36.6	3
10	3.3	37.5	3.4	37.8	1	3.4	38.2	3
11	3.4	38.9	3.4	39.4	1	3.4	39.9	2
12	3.3	40.2	3.5	40.6	1	3.4	41.2	2
13	3.3	41.7	3.4	41.8	1	3.5	42.4	2
17	3.1	46.7	3.3	46.5	1	3.3	47.2	2
21	3.4	48.9	3.6	48.7	1	3.6	49.2	2
25	3.7	50.1	3.8	49.9	1	3.9	50.2	2
29	3.9	51.4	4.3	51.8	1	4.1	51.8	2
33	3.9	52.2	4.1	52.6	1	4.2	52.5	2
37	4.0	52.7	4.2	52.7	1	4.6	52.7	3
41	4.2	53.8	4.4	53.8	1	4.6	53.7	3
45	4.2	53.8	4.4	53.6	1	4.7	53.9	3
49	4.2	54.5	4.6	54.6	1	4.6	54.7	2
53	4.4	55.2	4.4	55.0	1	4.6	55.0	2
57	4.3	55.5	4.7	55.2	1	4.7	55.2	2
61	4.9	55.1	4.9	54.9	1	5.0	54.1	3
65	4.8	55.3	4.8	55.0	1	4.8	54.4	3
69	5.4	55.6	5.2	55.2	1	5.0	54.2	3
73	5.1	55.1	5.1	53.7	1	5.1	53.6	3
77	5.0	54.0	4.9	52.6	1	5.0	52.9	3
81	4.9	54.3	5.0	52.5	1	4.9	53.1	3
85	4.7	53.0	4.7	52.1	1	4.6	52.3	3
89	4.6	52.0	4.5	51.6	1	4.6	50.7	3
93	4.7	51.7	4.6	50.0	1	4.8	49.3	3
97	4.7	51.7	4.9	50.5	1	5.1	48.8	3
101	4.5	50.3	5.0	49.9	1	4.9	46.9	3
Mean for weeks								
1-13	3.6	32.8	3.7	33.0	2	3.7	33.3	3
14-52	3.8	51.6	4.1	51.6	1	4.2	51.8	2
53-101	4.8	53.8	4.8	52.9	1	4.9	52.3	3

TABLE G3
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	85.7 mg/L			257.4 mg/L		
	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	3.7	23.2	14	2.7	23.2	30
2	3.5	25.2	12	2.7	24.4	29
3	3.5	26.6	11	2.5	25.4	25
4	3.5	27.8	11	2.5	26.3	25
5	3.5	29.5	10	2.6	27.5	24
6	3.5	31.0	10	2.6	28.6	23
7	3.6	32.1	10	2.5	29.5	22
8	3.5	33.6	9	2.5	30.4	21
9	3.5	35.0	9	2.4	31.4	20
10	3.3	36.5	8	2.5	32.2	20
11	3.3	37.9	8	2.4	33.3	19
12	3.2	39.1	7	2.5	34.4	19
13	3.1	40.4	7	2.4	35.2	18
17	3.1	45.1	6	2.4	38.9	16
21	3.4	47.9	6	2.7	42.2	17
25	3.3	49.5	6	2.5	44.5	15
29	3.7	51.6	6	2.7	47.4	15
33	3.7	51.8	6	2.5	48.3	13
37	3.8	52.4	6	2.7	48.9	14
41	3.9	53.3	6	2.7	49.7	14
45	3.9	53.5	6	2.6	49.9	13
49	4.0	54.4	6	2.7	50.4	14
53	3.9	54.4	6	2.7	50.8	14
57	4.0	55.0	6	2.8	50.9	14
61	4.1	54.6	6	2.8	50.8	14
65	4.2	55.1	7	2.9	50.8	15
69	4.3	55.1	7	3.1	50.9	16
73	4.4	54.4	7	3.1	50.3	16
77	4.2	53.8	7	3.3	49.9	17
81	4.2	52.8	7	3.2	49.8	17
85	3.9	52.1	6	3.3	48.8	17
89	3.8	51.3	6	3.1	49.3	16
93	4.1	49.0	7	3.1	49.3	16
97	4.3	48.6	8	3.3	48.1	18
101	4.3	48.4	8	3.5	47.2	19
Mean for weeks						
1-13	3.4	32.1	10	2.5	29.4	23
14-52	3.6	51.1	6	2.6	46.7	15
53-101	4.1	52.7	7	3.1	49.8	16

[a] Grams of drinking water consumed per animal per day
[b] Milligrams of sodium dichromate dihydrate consumed per kilogram body weight per day

TABLE G4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	0 mg/L		14.3 mg/L			57.3 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	2.9	17.8	2.9	17.5	2	2.8	17.4	9
2	3.0	19.2	3.0	19.2	2	2.8	19.0	8
3	3.2	20.6	3.1	20.6	2	2.8	20.3	8
4	3.1	21.3	3.2	21.4	2	2.9	21.0	8
5	3.3	22.5	3.2	22.3	2	3.0	21.8	8
6	3.1	23.2	3.2	23.2	2	2.9	22.7	7
7	3.5	24.4	3.3	24.4	2	3.0	23.8	7
8	3.1	26.0	3.2	25.4	2	3.1	24.8	7
9	3.2	26.9	3.3	26.4	2	3.2	25.4	7
10	3.1	27.9	3.3	27.4	2	2.9	26.2	6
11	3.1	28.9	3.3	28.3	2	3.3	27.1	7
12	3.2	30.3	3.3	29.7	2	3.4	28.6	7
13	3.1	31.2	3.1	31.0	1	3.0	29.7	6
17	2.8	37.0	3.0	36.9	1	3.0	34.4	5
21	2.6	41.5	2.6	41.3	1	2.6	38.5	4
25	2.3	44.8	2.5	44.9	1	2.8	41.9	4
29	2.6	48.7	2.5	48.2	1	2.6	46.5	3
33	2.6	51.6	2.5	51.7	1	2.5	48.8	3
37	2.5	53.3	2.8	53.6	1	2.5	50.6	3
41	2.8	55.2	2.8	55.6	1	2.3	52.5	3
45	2.4	59.0	2.5	57.9	1	2.3	55.1	2
49	2.7	59.8	2.7	59.0	1	2.8	56.7	3
53	2.6	62.1	2.5	62.1	1	2.3	60.0	2
57	2.6	61.5	2.6	60.9	1	2.4	59.0	2
61	2.5	62.2	2.5	62.5	1	2.4	60.1	2
65	2.6	63.1	2.6	62.8	1	2.4	61.6	2
69	2.6	64.3	2.6	64.8	1	2.4	62.7	2
73	2.9	63.9	2.7	65.0	1	2.4	62.4	2
77	2.5	62.7	2.4	64.0	1	2.2	61.6	2
81	2.9	61.8	2.6	62.9	1	2.3	60.8	2
85	2.4	61.3	2.5	62.7	1	2.7	59.8	3
89	2.7	60.3	2.7	62.1	1	2.3	59.7	2
93	2.9	60.6	3.0	61.1	1	2.4	58.5	2
97	3.5	59.1	3.5	60.2	1	2.7	58.1	3
101	3.1	60.6	3.6	60.7	1	2.6	58.1	3
Mean for weeks								
1-13	3.1	24.6	3.2	24.4	2	3.0	23.7	7
14-52	2.6	50.1	2.7	49.9	1	2.6	47.2	3
53-101	2.8	61.8	2.8	62.4	1	2.4	60.2	2

TABLE G4
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate

Weeks on Study	172 mg/L			516 mg/L		
	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
1	2.5	17.7	24	1.6	17.5	47
2	2.2	19.1	20	1.7	18.4	48
3	2.2	20.2	19	1.6	19.3	43
4	2.2	20.8	18	1.8	19.9	47
5	2.6	21.5	21	1.7	20.8	42
6	2.3	22.4	18	1.7	21.3	41
7	2.8	23.1	21	2.0	22.3	46
8	2.6	23.9	19	1.9	23.3	42
9	2.4	24.6	17	1.9	23.8	41
10	2.5	25.2	17	1.9	24.6	40
11	2.4	25.8	16	1.9	24.7	40
12	2.5	26.8	16	1.9	25.5	39
13	2.5	27.5	16	1.9	26.2	37
17	2.3	31.4	13	1.9	28.6	34
21	3.0	35.1	15	1.9	30.8	32
25	2.2	37.6	10	1.8	32.8	28
29	2.4	41.5	10	1.9	36.0	27
33	2.2	43.7	9	2.0	37.5	28
37	2.2	45.5	8	1.9	38.9	25
41	2.3	47.8	8	2.0	41.0	25
45	2.1	50.4	7	1.8	43.9	21
49	2.3	52.7	8	1.9	45.4	22
53	2.0	55.4	6	1.9	48.1	20
57	2.1	55.8	7	1.9	48.4	20
61	2.1	57.1	6	1.9	49.2	20
65	2.1	57.7	6	1.9	50.0	20
69	2.0	59.1	6	2.0	51.9	20
73	2.0	58.4	6	1.8	51.9	18
77	1.9	57.7	6	2.0	51.9	20
81	2.1	57.6	6	1.8	51.8	18
85	2.0	57.1	6	1.7	51.2	17
89	2.0	57.5	6	1.8	51.6	18
93	2.0	56.0	6	1.9	50.3	20
97	2.4	56.1	7	2.2	50.8	22
101	2.2	55.8	7	2.0	51.4	20
Mean for weeks						
1-13	2.4	23.0	19	1.8	22.1	43
14-52	2.3	42.9	10	1.9	37.2	27
53-101	2.1	57.0	6	1.9	50.7	19

[a] Grams of drinking water consumed per animal per day
[b] Milligrams of sodium dichromate dihydrate consumed per kilogram body weight per day

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

TABLE H1
Ingredients of NTP-2000 Rat and Mouse Ration

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

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

TABLE H2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

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

[a] Per kg of finished product

TABLE H3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.8 ± 0.45	13.8 – 15.8	26
Crude fat (% by weight)	8.1 ± 0.35	7.4 – 9.0	26
Crude fiber (% by weight)	9.1 ± 0.45	8.2 – 9.9	26
Ash (% by weight)	5.0 ± 0.24	4.4 – 5.6	26
Amino Acids (% of total diet)			
Arginine	0.750 ± 0.048	0.670 – 0.850	15
Cystine	0.225 ± 0.025	0.150 – 0.250	15
Glycine	0.701 ± 0.039	0.620 – 0.750	15
Histidine	0.365 ± 0.090	0.310 – 0.680	15
Isoleucine	0.533 ± 0.038	0.430 – 0.590	15
Leucine	1.077 ± 0.059	0.960 – 1.150	15
Lysine	0.703 ± 0.125	0.310 – 0.830	15
Methionine	0.402 ± 0.049	0.260 – 0.460	15
Phenylalanine	0.615 ± 0.035	0.540 – 0.660	15
Threonine	0.492 ± 0.040	0.430 – 0.590	15
Tryptophan	0.135 ± 0.018	0.110 – 0.160	15
Tyrosine	0.378 ± 0.048	0.280 – 0.460	15
Valine	0.658 ± 0.043	0.550 – 0.710	15
Essential Fatty Acids (% of total diet)			
Linoleic	3.90 ± 0.256	3.49 – 4.54	15
Linolenic	0.30 ± 0.035	0.21 – 0.35	15
Vitamins			
Vitamin A (IU/kg)	5,031 ± 115	3,400 – 8,900	26
Vitamin D (IU/kg)	1,000[a]		
ὰ-Tocopherol (ppm)	84.2 ± 16.60	52.0 – 110.0	15
Thiamine (ppm)[b]	8.7 ± 3.58	5.9 – 25.2	26
Riboflavin (ppm)	6.8 ± 2.11	4.20 – 11.20	15
Niacin (ppm)	79.0 ± 10.50	66.4 – 98.2	15
Pantothenic acid (ppm)	23.9 ± 3.73	17.4 – 29.8	15
Pyridoxine (ppm)[b]	9.21 ± 2.20	6.4 – 13.7	15
Folic acid (ppm)	1.75 ± 0.54	1.20 – 3.27	15
Biotin (ppm)	0.332 ± 0.12	0.225 – 0.704	15
Vitamin B_{12} (ppb)	60.5 ± 46.5	18.3 – 174.0	15
Choline (ppm)[b]	3,064 ± 270	2,700 – 3,790	15
Minerals			
Calcium (%)	0.964 ± 0.047	0.873 – 1.050	26
Phosphorus (%)	0.585 ± 0.027	0.538 – 0.641	26
Potassium (%)	0.665 ± 0.023	0.626 – 0.694	15
Chloride (%)	0.376 ± 0.041	0.300 – 0.474	15
Sodium (%)	0.191 ± 0.017	0.160 – 0.222	15
Magnesium (%)	0.201 ± 0.009	0.185 – 0.217	15
Sulfur (%)	0.170 ± 0.029	0.116 – 0.209	15
Iron (ppm)	182 ± 46.7	135 – 311	15
Manganese (ppm)	54.1 ± 7.89	42.1 – 73.1	15
Zinc (ppm)	55.0 ± 9.55	43.3 – 78.5	15
Copper (ppm)	6.65 ± 1.790	3.21 – 10.50	15
Iodine (ppm)	0.512 ± 0.221	0.233 – 0.972	15
Chromium (ppm)	0.604 ± 0.253	0.330 – 1.380	14
Cobalt (ppm)	0.25 ± 0.074	0.20 – 0.47	14

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

TABLE H4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.38 ± 0.158	0.14 – 0.50	26
Cadmium (ppm)	0.07 ± 0.022	0.04 – 0.10	26
Lead (ppm)	0.08 ± 0.031	0.05 – 0.17	26
Mercury (ppm)	<0.02		26
Selenium (ppm)	0.19 ± 0.027	0.14 – 0.23	26
Aflatoxins (ppb)	<5.00		26
Nitrate nitrogen (ppm)[c]	15.2 ± 4.09	10.0 – 24.4	26
Nitrite nitrogen (ppm)[c]	<0.61		26
BHA (ppm)[d]	<1.0		26
BHT (ppm)[d]	<1.0		26
Aerobic plate count (CFU/g)	25 ± 68	10 – 360	26
Coliform (MPN/g)	0.3 ± 0.0	3.0 – 3.0	26
Escherichia coli (MPN/g)	<10		26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[e]	4.3 ± 1.93	2.3 – 8.5	26
N-Nitrosodimethylamine (ppb)[e]	2.6 ± 1.68	1.1 – 6.9	26
N-Nitrosopyrrolidine (ppb)[e]	1.7 ± 0.74	0.9 – 4.1	26
Pesticides (ppm)			
α-BHC	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.10		26
Estimated PCBs	<0.20		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl chlorpyrifos	0.082 ± 0.069	0.020 – 0.259	26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.284 ± 0.477	0.020 – 1.850	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

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

APPENDIX I
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.

During the 2-year study, serum samples were collected from five or six male and five female sentinel rats and mice at 6, 12, and 18 months; from five male and five female rats and five female mice in the 516 mg/L group at study termination; and from five male mice in the 257.4 mg/L group at study termination. In addition, serum samples were collected from six male and five female treated rats at 19 months, and fecal samples were collected from five male and five female mice at 18 months. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to BioReliance Corporation (Rockville, MD) for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
Rats	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, 18, and 19 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination
Sendai	18 and 19 months
Western Blot	
Sendai	18 months

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

Results of serology tests are presented in Table I1.

TABLE I1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Drinking Water Studies of Sodium Dichromate Dihydrate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	1/11[a]	Sendai
19 Months	0/11	None positive
Study termination	0/10	None positive
Mice		
6 Months	0/10	None positive
12 Months	0/10	None positive
18 Months	0/10	None positive
Study termination	0/10	None positive

[a] Based on retesting of serum samples at 19 months, this most likely represents a false positive result in one rat. There was no evidence of infection by a viral organism in these animals.

APPENDIX J
CHROMIUM TISSUE DISTRIBUTION STUDY

CHROMIUM TISSUE DISTRIBUTION STUDY

MATERIALS AND METHODS

Groups of 40 special study male rats and female mice were randomly assigned to the tissue distribution study at the beginning of the 2-year study and treated identically to the core study groups. On days 4, 11, 180, and 369, up to 10 animals per exposure group were removed from treatment and placed in individual metabolism cages to allow separate collection of urine and feces. The animals had access to undosed water and feed *ad libitum*. Two collections of urine and feces were made to include the intervals from 0 to 24 and 24 to 48 hours; measured values were combined to yield the reported 48-hour values. Urine and feces collections were frozen at –20° C and shipped to the analytical laboratory (RTI International, Research Triangle Park, NC).

At the end of 48 hours, the animals were anesthetized with CO_2/O_2, and blood was taken from the retroorbital sinus into heparinized centrifuge tubes. The blood was separated into cells and plasma. While the animals were still under CO_2/O_2 anesthesia, the abdominal wall was opened and the aorta was severed. The entire liver, both kidneys, and the stomach (separated into glandular and forestomach parts) were removed, weighed, and frozen at –20° C and shipped frozen to the analytical laboratory. Stainless steel was avoided during the tissue collection; only plastic, Teflon™, ceramic, or tungsten carbide instruments were used.

The tissue samples were stored in a freezer. Prior to homogenization, the samples were allowed to thaw at room temperature in a Class 100 environment. Tissue samples were added to tared glass scintillation vials, and the whole wet tissue mass was recorded. A minimal amount of deionized water was added to each sample, and the total mass (tissue plus deionized water) was recorded. Each tissue sample was homogenized using a Polytron tissue homogenizer (Brinkmann Instruments, Westbury, NY) and returned to frozen storage.

Prior to aliquot transfer, the tissue homogenate was removed from frozen storage and allowed to thaw at room temperature in a Class 100 environment. Each tissue homogenate was mixed well to ensure complete homogeneity. An aliquot of homogenate containing approximately 0.500 g of tissue was transferred to a tared 50 mL centrifuge tube, and the mass was recorded. Approximately 5% of the rat kidney samples were prepared with duplicate aliquots, and masses were recorded. The actual mass for each sample was calculated by applying the percent tissue in the homogenate to the measured mass. Homogenization was not necessary if the tissue mass was less than 0.500 g, but duplicate aliquots for these samples could not be prepared.

Five mL of concentrated nitric acid was added to each centrifuge tube containing tissue. The tubes were capped with microwavable caps and allowed to stand overnight at room temperature. The following morning, 2 mL of deionized water was added to each centrifuge tube. The tubes were arranged in a microwave tray; the thermowell and temperature sensors were inserted into one of the sample tubes to monitor the digestion; and the samples were subjected to a four-stage microwave digestion program that ramped the power from 60% to 100% with hold times of 5 to 20 minutes. Samples achieved a maximum temperature of 110° C, which was held for 10 minutes.

After the digestion was complete, the samples were allowed to cool to room temperature. To each tube, 0.500 mL of hydrogen peroxide and 0.125 mL of hydrofluoric acid were added as was more deionized water, if necessary, to avoid charring. The samples were subjected to the same microwave program a second time and then allowed to cool. The content of each tube was transferred to a 25 mL volumetric flask, and 0.250 mL of a previously prepared 1.00 µg/mL internal standard solution was added. The internal standard solution was prepared by transferring 100 µL aliquots of NIST-traceable yttrium, bismuth, indium, and scandium stock solutions (1,000 µg/mL) to a 100 mL volumetric flask, adding 1 mL of concentrated nitric acid, and diluting to volume with deionized water. The tubes were rinsed with deionized water, and the rinses were added to the flasks. Each flask was brought to volume with deionized water and mixed well. Samples were transferred to clean plastic storage bottles and stored in a refrigerator until the day of analysis.

The solvent standards, digested matrix standards, and experimental samples were analyzed by inductively coupled

plasma-mass spectrometry using a Thermo X7 instrument (ThermoElectron Corp., Winsford, Cheshire, U.K.) or a Plasma Quad XR Instrument (VG Elemental Ltd., Winsford, Cheshire, U.K.) with a concentric nebulizer and a Peltier impact-bead spray chamber cooled to 5° C. A calibration curve was constructed at the beginning of each analysis, and the performance of the calibration was evaluated prior to sample analysis. A successful calibration was indicated by an acceptable correlation coefficient ($r > 0.99$) and residual percent read-backs within 20% of the lowest standard and within 10% of all other solvent standards. A valid calibration included a minimum of six calibration standards and a calibration blank.

Analysis data were considered valid if they were bracketed by valid quality control (QC) sets. A maximum of 10 samples (including method blanks and controls) were bracketed by a QC set, which consisted of the calibration blank and two midlevel calibration standards. A QC set passed when the measured concentration for one midlevel calibration standard was within 10% of its nominal value. This selected midlevel calibration standard was then required to pass consistently throughout the analysis. If the selected midlevel calibration standard failed, it was necessary to reanalyze the bracketed samples. Samples with responses greater than the calibration range were diluted with diluent solution to get a response within the range. The diluent solution was prepared by adding 1 mL of the internal standard solution and 20 mL of concentrated nitric acid to a 100 mL plastic volumetric flask and diluting to volume with deionized water.

TABLE J1
Tissue Concentrations and Excreta Content of Chromium in Male Rats in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n	3	3	3	3	3
Erythrocytes (µg/g)					
Day 6	0.044 ± 0.002	0.051 ± 0.002	0.126 ± 0.012*	0.252 ± 0.022*	0.391 ± 0.012**
Day 13	0.051 ± 0.002	0.036 ± 0.005	0.203 ± 0.019	0.504 ± 0.066*	0.899 ± 0.134**
Day 182	0.050 ± 0.014	0.054 ± 0.003	0.208 ± 0.002	0.591 ± 0.014*	0.997 ± 0.051**
Day 371	0.055 ± 0.003	0.064 ± 0.006*	0.160 ± 0.059**	0.526 ± 0.031**	0.693 ± 0.029**
Plasma (µg/g)[b]					
Day 6	0.052 ± 0.003	0.068 ± 0.007*	0.079 ± 0.003**	0.087 ± 0.008**	0.109 ± 0.007**
Day 13	0.054 ± 0.004	0.048 ± 0.006	0.079 ± 0.005*	0.103 ± 0.008**	0.146 ± 0.008**
Day 182	0.063 ± 0.005	0.064 ± 0.003	0.081 ± 0.004*	0.099 ± 0.007**	0.146 ± 0.009**
Day 371	0.054 ± 0.014	0.062 ± 0.005	0.071 ± 0.011	0.110 ± 0.010**	0.146 ± 0.003**
Liver (µg/g)					
Day 6	0.072 ± 0.007	0.097 ± 0.015	0.326 ± 0.027*	1.116 ± 0.200**	1.589 ± 0.125**
Day 13	0.080 ± 0.013	0.080 ± 0.005	0.700 ± 0.065	1.899 ± 0.347*	3.239 ± 0.385**
Day 182	0.081 ± 0.004	0.249 ± 0.007*	1.568 ± 0.040**	4.101 ± 0.110**	6.650 ± 0.249**
Day 371	0.092 ± 0.003	0.289 ± 0.029*	1.145 ± 0.334**	4.383 ± 0.419**	7.735 ± 0.155**
Kidney (µg/g)					
Day 6	0.376 ± 0.070	0.252 ± 0.049	0.591 ± 0.043	1.122 ± 0.087*	1.570 ± 0.024**
Day 13	0.089 ± 0.006	0.225 ± 0.009*	1.125 ± 0.041**	2.556 ± 0.390**	4.409 ± 0.596**
Day 182	0.083 ± 0.003	1.153 ± 0.036*	5.464 ± 0.054**	10.847 ± 0.195**	15.263 ± 0.280**
Day 371	0.170 ± 0.011	1.564 ± 0.055*	4.879 ± 1.259**	13.423 ± 0.307**	18.530 ± 0.430**
Glandular stomach (µg/g)					
Day 6	0.076 ± 0.003	0.143 ± 0.008*	0.333 ± 0.040**	0.773 ± 0.105**	1.967 ± 0.109**
Day 13	0.095 ± 0.008	0.254 ± 0.073*	0.310 ± 0.049*	1.331 ± 0.060**	1.762 ± 0.042**
Day 182	0.197 ± 0.031	0.414 ± 0.012*	1.043 ± 0.081**	4.300 ± 0.367**	9.886 ± 0.354**
Day 371	0.253 ± 0.066	0.334 ± 0.029	1.038 ± 0.115*	4.801 ± 0.345**	14.643 ± 0.121**
Forestomach (µg/g)					
Day 6	0.098 ± 0.024	0.076 ± 0.004	0.122 ± 0.008	0.294 ± 0.029	0.285 ± 0.123
Day 13	0.091 ± 0.015	0.102 ± 0.034	0.171 ± 0.050	0.221 ± 0.055*	0.593 ± 0.159**
Day 182	0.089 ± 0.018	0.099 ± 0.003	0.338 ± 0.022*	0.574 ± 0.171*	1.654 ± 0.244**
Day 371	0.090 ± 0.015	0.118 ± 0.008	0.328 ± 0.081*	1.338 ± 0.444**	2.849 ± 0.975**
Feces (µg)[c,d]					
Day 6	11.56 ± 3.06	26.87 ± 5.56*	122.29 ± 5.49**	246.86 ± 84.73**	1,030.2 ± 117.71**
Day 13	9.056 ± 1.977	52.335 ± 6.275*	171.734 ± 9.232**	362.994 ± 74.118**	972.867 ± 54.316**
Day 182	10.04 ± 2.06	63.64 ± 6.07*	229.71 ± 17.38**	467.84 ± 33.30**	1,947.6 ± 287.25**
Day 371	6.869 ± 1.126	36.299 ± 4.185*	139.488 ± 11.446*[e]	311.849 ± 10.293**	1,146.27 ± 114.235**
Urine (µg)[c,d]					
Day 6	0.275 ± 0.073	0.480 ± 0.053*	2.520 ± 0.732**	4.594 ± 1.118**	6.967 ± 0.717**
Day 13	0.139 ± 0.028	0.396 ± 0.114*	1.100 ± 0.253**	1.943 ± 0.390**	4.561 ± 0.486**
Day 182	0.630 ± 0.131	1.145 ± 0.101*	7.076 ± 0.075**	12.580 ± 0.898**	20.137 ± 0.579**
Day 371	0.588 ± 0.087	2.023 ± 0.267*	7.406 ± 1.020**	13.702 ± 2.107**	23.969 ± 3.875**

* Significantly different ($P \le 0.05$) from the control group by Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=6 for all plasma values
[c] Cumulative chromium content for 48 hours ending on the day indicated
[d] Measured values less than the experimental limit of quantitation (ELOQ) (2.00 µg Cr/g feces; 0.100 µg Cr/g urine) were included in the analysis as ½ ELOQ × sample mass.
[e] n=2

TABLE J2
Tissue Concentrations and Excreta Content of Chromium in Female Mice in the 2-Year Drinking Water Study of Sodium Dichromate Dihydrate[a]

	0 mg/L	14.3 mg/L	57.3 mg/L	172 mg/L	516 mg/L
n	3	3	3	3	3
Erythrocytes (µg/g)					
Day 6	0.040 ± 0.003	0.056 ± 0.010	0.108 ± 0.009*	0.260 ± 0.047**	0.374 ± 0.078**
Day 13	0.043 ± 0.005	0.042 ± 0.002	0.341 ± 0.100	0.747 ± 0.087*	1.190 ± 0.137**
Day 182	0.058 ± 0.004	0.079 ± 0.008	0.194 ± 0.016*	0.719 ± 0.052**	1.561 ± 0.165**
Day 371	0.036 ± 0.004	0.042 ± 0.011	0.094 ± 0.002	0.340 ± 0.020*	0.795 ± 0.089**
Plasma (µg/g)[b]					
Day 6	0.064 ± 0.006	0.075 ± 0.016	0.111 ± 0.026	0.150 ± 0.039**	0.213 ± 0.059**
Day 13	0.034 ± 0.016	0.038 ± 0.018	0.133 ± 0.024**	0.204 ± 0.045**	0.311 ± 0.077**
Day 182	0.051 ± 0.006	0.070 ± 0.010	0.116 ± 0.005**	0.167 ± 0.009**	0.253 ± 0.016**
Day 371	0.065 ± 0.004	0.086 ± 0.010	0.118 ± 0.014**	0.150 ± 0.012**	0.209 ± 0.009**
Liver (µg/g)					
Day 6	0.098 ± 0.039	0.340 ± 0.010*	1.421 ± 0.146**	4.638 ± 0.950**	5.622 ± 0.795**
Day 13	0.126 ± 0.003	0.591 ± 0.027*	2.659 ± 0.094**	9.374 ± 0.892**	14.830 ± 2.347**
Day 182	0.147 ± 0.015	0.746 ± 0.068*	4.575 ± 0.559**	17.270 ± 2.746**	52.047 ± 2.890**
Day 371	0.069 ± 0.007	0.792 ± 0.019*	3.782 ± 0.143**	13.777 ± 0.951**	39.450 ± 1.655**
Kidney (µg/g)					
Day 6	0.095 ± 0.011	0.166 ± 0.011*	0.415 ± 0.020**	0.892 ± 0.106**	1.338 ± 0.157**
Day 13	0.127 ± 0.032	0.245 ± 0.003*	1.259 ± 0.051**	4.061 ± 0.718**	4.027 ± 0.286**
Day 182	0.067 ± 0.006	0.361 ± 0.061*	2.062 ± 0.191**	10.187 ± 1.078**	17.487 ± 0.500**
Day 371	0.070 ± 0.002	0.340 ± 0.014*	1.291 ± 0.064**	7.868 ± 0.510**	21.827 ± 2.446**
Glandular stomach (µg/g)					
Day 6	0.306 ± 0.056	0.645 ± 0.253	1.258 ± 0.290*	2.450 ± 0.266**	5.785 ± 0.131**
Day 13	0.207 ± 0.053	0.324 ± 0.030	2.614 ± 0.190*	7.048 ± 1.751**	13.130 ± 2.604**
Day 182	0.305 ± 0.078	0.644 ± 0.035*	3.659 ± 0.547**	11.520 ± 3.017**	52.673 ± 12.310**
Day 371	0.731 ± 0.306	0.676 ± 0.104	2.807 ± 0.330*	9.994 ± 1.079*	49.867 ± 12.251**
Forestomach (µg/g)					
Day 6	0.328 ± 0.132	0.683 ± 0.262	1.308 ± 0.553	1.102 ± 0.373	1.286 ± 0.116
Day 13	0.201 ± 0.094	0.288 ± 0.056	0.400 ± 0.044	2.030 ± 0.532*	3.849 ± 1.811*
Day 182	0.173 ± 0.064	0.444 ± 0.099	1.033 ± 0.102*	2.141 ± 0.643**	9.624 ± 3.638**
Day 371	0.320 ± 0.049	0.381 ± 0.077	1.271 ± 0.300*	1.812 ± 0.208*	7.442 ± 0.764**
Feces (µg)[c,d]					
Day 6	2.598 ± 0.899	9.364 ± 1.422*	12.869 ± 2.918*	43.632 ± 10.221**	162.588 ± 31.040**
Day 13	2.348 ± 1.173	12.103 ± 3.355*	85.798 ± 21.386**	46.865 ± 4.905*	107.822 ± 30.842**
Day 182	1.275 ± 0.568	5.266 ± 0.425*	17.633 ± 3.070**	24.583 ± 5.796**	122.734 ± 21.606**
Day 371	7.484 ± 2.862	9.502 ± 1.566	18.682 ± 2.165*	40.853 ± 3.288**	72.071 ± 19.116**
Urine (µg)[c,d]					
Day 6	0.034 ± 0.007	0.122 ± 0.033*	0.347 ± 0.152*[e]	—[f]	—
Day 13	0.020 ± 0.008	0.233 ± 0.009[e]	0.501[g]	—	2.190 ± 0.126*[e]
Day 182	0.089 ± 0.051	0.145 ± 0.035[e]	0.648 ± 0.213*	1.339 ± 0.199*[e]	—
Day 371	0.074 ± 0.008	0.470 ± 0.103*	1.343 ± 0.234**	3.953 ± 1.460**[e]	3.251 ± 1.263**

* Significantly different ($P \leq 0.05$) from the control group by Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=6 for all plasma values
[c] Cumulative chromium content for 48 hours ending on the day indicated
[d] Measured values less than the experimental limit of quantitation (ELOQ) (2.00 µg Cr/g feces; 0.100 µg Cr/g urine) were included in the analysis as ½ ELOQ × sample mass.
[e] n=2
[f] Data not available
[g] n=1