NTP REPORT

ON THE

TOXICOLOGY STUDIES OF SODIUM BROMATE

(CAS NO. 7789-38-0)

IN GENETICALLY MODIFIED (FVB Tg.AC HEMIZYGOUS) MICE

(DERMAL AND DRINKING WATER STUDIES)

AND CARCINOGENICITY STUDIES OF SODIUM BROMATE IN GENETICALLY MODIFIED [B6.129-*Trp53*^{tm1Brd} (N5) HAPLOINSUFFICIENT] MICE

(DRINKING WATER STUDIES)

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

March 2007

NTP GMM 6

NIH Publication No. 07-4423

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 Genetically Modified Model (GMM) Report series began in 2005 with studies conducted by the NTP. The studies described in the GMM Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected agents in laboratory animals that have been genetically modified. These genetic modifications may involve inactivation of selected tumor suppressor functions or activation of oncogenes that are commonly observed in human cancers. This may result in a rapid onset of cancer in the genetically modified animal when exposure is to agents that act directly or indirectly on the affected pathway. An absence of a carcinogenic response may reflect either an absence of carcinogenic potential of the agent or that the selected model does not harbor the appropriate genetic modification to reduce tumor latency and allow detection of carcinogenic activity under the conditions of these subchronic studies. 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 GMM 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 GMM 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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CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

M.J. Hooth, Ph.D., Study Scientist
J.C. Peckham, D.V.M., M.S., Ph.D., Study Pathologist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
L.T. Burka, Ph.D.
R.S. Chhabra, Ph.D.
J.E. French, Ph.D.
R.A. Herbert, D.V.M., Ph.D.
A.P. King-Herbert, D.V.M.
G.E. Kissling, Ph.D.
D.E. Malarkey, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
S.D. Peddada, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
M.K. Vallant, B.S., M.T.
K.L. Witt, M.S.

Battelle Columbus Operations

Conducted studies and evaluated pathology findings

M.R. Hejtmancik, Ph.D., Principal Investigator
J.D. Johnson, Ph.D.
M.J. Ryan, D.V.M., Ph.D.

Experimental Pathology Laboratories, Inc.

Provided pathology review

M.H. Hamlin, II, D.V.M., Principal Investigator
K.J. Cimon, D.V.M., M.S.
P.C. Howroyd, M.A., Vet.M.B.
J.C. Peckham, D.V.M., M.S., Ph.D.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides and prepared pathology report on mice (July 16, 2002)

S. Rouselle, D.V.M., Chairperson
Pathology Associates, A Charles River Company
K.J. Cimon, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
P.C. Howroyd, M.A., Vet.M.B.
Experimental Pathology Laboratories, Inc.
G. Pearse, B.V.M. & S.
National Toxicology Program
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
D. Wolf, D.V.M., Ph.D.
Environmental Protection Agency

Constella Group, Inc.

Provided statistical analyses

P.W. Crockett, Ph.D., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.

Biotechnical Services, Inc.

Prepared Report

S.R. Gunnels, M.A., Principal Investigator
P.H. Carver, B.A.
B.F. Hall, M.S.
L.M. Harper, B.S.
D.C. Serbus, Ph.D.

CONTENTS

SUMMARY

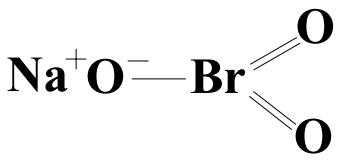
Background
Sodium bromate is a by-product of water disinfection. We tested if sodium bromate could cause cancer in two different strains of genetically modified mice.

Methods
We applied solutions containing sodium bromate to the backs of male and female Tg.AC mice for 6 or 9 months, and gave sodium bromate dissolved in drinking water to male and female Tg.AC and p53 mice for 6 or 10 months. The ethanol/water vehicle without any chemical was applied to the backs of control mice in the dermal studies, and animals given plain water served as the control groups for the drinking water studies. Tissues from 15 sites were examined for every animal.

Results
Exposure to sodium bromate either through the skin or by drinking water decreased body weights in groups given the highest concentrations. No increases in tumors were seen in males or females from either strain of mice.

Conclusions
We conclude that sodium bromate did not cause cancer in the genetically modified mice used in these studies. This chemical did cause cancer in other studies with different rodents, and thus these genetically modified mice may not be as sensitive for detecting certain cancer-causing compounds.

ABSTRACT



SODIUM BROMATE

CAS No. 7789-38-0

Chemical Formula: $NaBrO_3$ Molecular Weight: 150.9

Synonyms: Bromic acid, sodium salt
Trade names: Dyetone, Neutralizer K-126, Neutralizer K-140, Neutralizer K-938

Bromate is a drinking water disinfection by-product formed during the ozonation of source water containing bromide. Sodium bromate is also used as an analytical reagent, in the oxidation of sulfur and vat dyes, and for cleaning boilers. As a mixture with sodium bromide, it is used for dissolving gold from its ores. The cosmetic industry uses sodium bromate and potassium bromate as neutralizers or oxidizers in hair wave preparations. Sodium bromate was nominated for toxicity and carcinogenicity studies in transgenic mouse models by the United States Environmental Protection Agency and the National Institute of Environmental Health Sciences. Male and female Tg.AC hemizygous mice received sodium bromate by dermal application for 26 or 39 weeks and by exposure in drinking water for 27 or 43 weeks. Male and female p53 haploinsufficient mice were exposed to sodium bromate (at least 99% pure) in drinking water for 27 or 43 weeks. Genetic toxicology studies were conducted in mouse peripheral blood erythrocytes.

26- and 39-Week Dermal Studies in Tg.AC Hemizygous Mice

Groups of 15 male and 15 female Tg.AC hemizygous mice received dermal applications of 0, 64, 128, or 256 mg sodium bromate/kg body weight in ethanol/water, 5 days per week for 26 weeks. Additional groups of 10 male and 10 female Tg.AC hemizygous mice were dermally administered the same doses for 39 weeks. Survival of dosed groups was similar to that of vehicle control groups at 26 and 39 weeks. Mean body weights of 256 mg/kg males were less than those of the vehicle control group in both studies. Mean body weights of all dosed groups of females were less than those of the vehicle controls at 39 weeks.

Minimal decreases in hematocrit and hemoglobin concentration values occurred in 128 mg/kg females and 256 mg/kg males and females at 26 weeks. A minimal decrease in erythrocyte count also occurred in 256 mg/kg males. These decreases in erythron were

accompanied by a minimal decrease in mean cell hemoglobin and mean cell hemoglobin concentration values, primarily in the females. Reticulocyte counts were significantly increased in 128 mg/kg females and 256 mg/kg males and females.

There were no increased incidences of neoplasms in male or female Tg.AC hemizygous mice exposed to sodium bromate dermally.

Relative kidney weights were significantly increased in 256 mg/kg males at 26 weeks and in all dosed groups of males at 39 weeks. Absolute testis weights in 256 mg/kg males and absolute kidney weights in 256 mg/kg females were decreased at 39 weeks. Nephropathy occurred in 14 of 15 males receiving 128 and 256 mg/kg at 26 weeks and in all 256 mg/kg females in both studies. In the thyroid gland, the incidences of follicular cell hypertrophy in all dosed groups of males and females, follicular secretory depletion in 128 and 256 mg/kg females, and lymphocytic cellular infiltrate in 256 mg/kg females were significantly increased in both studies. Splenic hematopoietic cell proliferation occurred with a significantly increased incidence in 128 and 256 mg/kg females at 26 weeks. The incidence of germinal epithelium degeneration in the testis was significantly increased in 256 mg/kg males at 39 weeks.

27- and 43-Week Drinking Water Studies in Tg.AC Hemizygous Mice

Groups of 15 male and 15 female Tg.AC hemizygous mice were exposed to drinking water containing 0, 80, 400, or 800 mg/L sodium bromate for 27 weeks (equivalent to average daily doses of approximately 13, 63, and 129 mg/kg to male mice and 15, 72, and 148 mg/kg to female mice). Additional groups of 10 male and 10 female Tg.AC hemizygous mice were exposed to drinking water containing 0, 80, 400, or 800 mg/L sodium bromate for 43 weeks (equivalent to average daily doses of approximately 11, 52, and 131 mg/kg to male mice and 15, 65, and 152 mg/kg to female mice). Survival of exposed groups was similar to that of control groups at 27 weeks. Survival was decreased in 400 mg/L females and 800 mg/L males and females at 43 weeks. Mean body weights of 400 mg/L males and 800 mg/L males and females were less than those of the control groups in both studies. Water consumption by exposed mice was generally similar to that by control groups throughout both studies.

Minimal decreases in hematocrit, hemoglobin concentration, and erythrocyte count values occurred primarily in 400 and 800 mg/kg females at 27 weeks. There were also decreases in mean cell hemoglobin and mean cell hemoglobin concentration values, but these occurred primarily in treated males. Reticulocyte counts were increased in 400 mg/kg males and 800 mg/kg males and females.

There were no increased incidences of neoplasms in male or female Tg.AC hemizygous mice exposed to sodium bromate in the drinking water.

Absolute kidney weights were significantly decreased in 800 mg/L females and relative kidney weights were increased in 400 and 800 mg/L males at 27 weeks. Absolute testis weights were significantly decreased in 800 mg/L males at 43 weeks. Thyroid gland follicular cell hypertrophy and follicular secretory depletion occurred in most 400 and 800 mg/L males and females at 27 weeks and in most exposed females at 43 weeks, and the incidences of thyroid gland follicular cell hypertrophy were significantly increased in all exposed groups of males at 43 weeks. The incidences of thyroid gland lymphocytic cellular infiltrates were significantly increased in 400 and 800 mg/L females in both studies and in 800 mg/L males at 43 weeks. The incidences of nephropathy were significantly increased in all exposed groups of males and in 400 and 800 mg/L females at 27 weeks. Renal tubule degeneration occurred with significantly increased incidences in 800 mg/L males and females in both studies. The incidences of renal tubule hypertrophy were significantly increased in 400 and 800 mg/L females at 27 weeks and in 800 mg/L males and females at 43 weeks. Pituitary gland pars distalis hypertrophy occurred with a significantly increased incidence in 800 mg/L females in both studies. The incidence of hyperkeratosis of the forestomach epithelium was significantly increased in 800 mg/L females at 43 weeks. The incidences of tubule degeneration of the epididymis and germinal epithelium degeneration of the testis were significantly increased in 800 mg/L males at 43 weeks.

27- and 43-Week Drinking Water Studies in p53 Haploinsufficient Mice

Groups of 15 male and 15 female p53 haploinsufficient mice were exposed to drinking water containing 0, 80, 400, or 800 mg/L sodium bromate for 27 weeks (equivalent to average daily doses of approximately 8, 39, and 74 mg/kg to males and 13, 72, and 136 mg/kg to females). Additional groups of 10 male and 10 female p53 haploinsufficient mice were exposed to drinking water containing 0, 80, 400, or 800 mg/L sodium bromate for 43 weeks (equivalent to average daily doses of approximately 7, 37, and 65 mg/kg to males and 11, 58, and 107 mg/kg to females). In both studies, survival of exposed groups was similar to that of control groups. Mean body weights of 400 and 800 mg/L females were less than those of the control groups during most of the studies. Water consumption by exposed mice was generally similar to that by control groups in both studies. No neoplasms or nonneoplastic lesions in male or female p53 haploinsufficient mice were attributed to exposure to sodium bromate in either study.

Genetic Toxicology

Sodium bromate exposure resulted in significantly increased frequencies of micronucleated erythrocytes in male and female Tg.AC hemizygous and p53 haploinsufficient mice administered the chemical in drinking water for 27 weeks or by dermal application for 26 weeks. Tg.AC hemizygous mice were treated by both routes; p53 haploinsufficient mice were exposed only through drinking water. In all three micronucleus tests, a clear dose response was observed in male and female mice. Significant increases in the percentage of polychromatic erythrocytes among total erythrocytes were observed in male and female Tg.AC hemizygous mice exposed via drinking water and in male Tg.AC hemizygous mice dosed dermally with sodium bromate. The percentage of polychromatic erythrocytes was not significantly altered in male or female p53 mice.

Conclusions

Under the conditions of these drinking water studies, there was *no evidence of carcinogenic activity** of sodium bromate in male or female p53 haploinsufficient mice exposed to 80, 400, or 800 mg/L for 27 or 43 weeks.

No treatment-related neoplasms were seen in male or female Tg.AC hemizygous mice exposed dermally to 64, 128, or 256 mg sodium bromate/kg body weight for 26 or 39 weeks.

No treatment-related neoplasms were seen in male or female Tg.AC hemizygous mice exposed by drinking water to 80, 400, or 800 mg sodium bromate/L for 27 or 43 weeks.

In drinking water and dermal studies in Tg.AC hemizygous mice there were increased incidences of nonneoplastic lesions in the thyroid gland and kidney.

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

Summary of the 26- and 39-Week Dermal and Genetic Toxicology Studies of Sodium Bromate in Tg.AC Hemizygous Mice

	Males		Females	
	26 Weeks	39 Weeks	26 Weeks	39 Weeks
Doses in ethanol/water	Vehicle control, 64, 128, or 256 mg/kg	Vehicle control, 64, 128, or 256 mg/kg	Vehicle control, 64, 128, or 256 mg/kg	Vehicle control, 64, 128, or 256 mg/kg
Body weights	256 mg/kg group less than the vehicle control group	128 and 256 mg/kg groups less than the vehicle control group	Dosed groups similar to the vehicle control group	Dosed groups less than the vehicle control group
Survival rates	12/15, 11/15, 13/15, 15/15	8/10, 8/10, 8/10, 8/10	11/15, 10/15, 11/15, 11/15	7/10, 7/10, 8/10, 8/10
Nonneoplastic effects	Thyroid gland: follicular cell hypertrophy (0/15, 7/15, 10/15, 14/15) Kidney: nephropathy (8/15, 8/15, 14/15, 14/15)	Thyroid gland: follicular cell hypertrophy (0/10, 9/10, 8/10, 8/10) Testes: gernimal epithelium degeneration (1/19, 2/10, 3/10, 6/10)	Thyroid gland: follicular cell hypertrophy (1/15, 9/15, 12/15, 13/15); follicular secretory depletion (6/15, 11/15, 13/15, 14/15); lymphocyte cellular infiltrates (0/15, 6/15, 3/15, 12/15) Kidney: nephropathy (8/15, 7/15, 13/15, 15/15) Spleen: hematopoietic cell proliferation (3/15, 5/15, 9/15, 10/15)	Thyroid gland: follicular cell hypertrophy (1/9, 9/10, 9/10, 10/10); follicular secretory depletion (5/9, 8/10, 10/10, 10/10); lymphocyte cellular infiltrates (0/9, 2/10, 5/10, 10/10) Kidney: nephropathy (5/9, 6/10, 8/10, 10/10)
Neoplastic effects	None	None	None	None
Genetic toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Positive in male and female Tg.AC hemizygous mice		

Summary of the 27- and 43-Week Drinking Water and Genetic Toxicology Studies of Sodium Bromate in Tg.AC Hemizygous Mice

	Males		Females	
	27 Weeks	**43 Weeks**	**27 Weeks**	**43 Weeks**
Concentrations in water	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L
Body weights	400 and 800 mg/L groups less than the control group	400 and 800 mg/L groups less than the control group	800 mg/L group less than the control group	80 and 800 mg/L groups less than the control group
Survival rates	13/15, 13/15, 14/15, 14/15	6/10, 7/10, 6/10, 4/10	10/15, 9/15, 10/15, 12/15	7/10, 5/10, 4/10, 2/10
Nonneoplastic effects	Thyroid gland: follicular cell hypertrophy (1/15, 2/14, 12/15, 15/15); follicular secretory depletion (4/15, 6/14, 15/15, 15/15) Kidney: nephropathy (1/15, 7/15, 10/15, 14/15); renal tubule degeneration (0/15, 0/15, 0/15, 10/15)	Thyroid gland: follicular cell hypertrophy (0/10, 6/10, 8/10, 8/9); lymphocytic cellular infiltrates (0/10, 0/10, 0/10, 4/9) Kidney: renal tubule degeneration (0/10, 0/10, 1/10, 8/10); renal tubule hypertrophy (0/10, 0/10, 1/10, 6/10) Epididymis: degeneration (1/10, 1/10, 0/10, 7/10) Testes: germinal epithelium degeneration (0/10, 0/10, 3/10, 8/10)	Thyroid gland: follicular cell hypertrophy (2/15, 2/13, 11/13, 13/15); follicular secretory depletion (7/15, 7/13, 11/13, 14/15); lymphocytic cellular infiltrates (0/15, 0/13, 5/13, 11/15) Kidney: nephropathy (2/15, 2/15, 10/15, 13/15); renal tubule degeneration (0/15, 0/15, 2/15, 8/15); renal tubule hypertrophy (0/15, 1/15, 5/15, 12/15) Pituitary gland: pars distalis hypertrophy (0/15, 0/15, 0/15, 6/15)	Thyroid gland: follicular cell hypertrophy (0/10, 8/9, 10/10, 10/10); follicular secretory depletion (1/10, 8/9, 9/10, 10/10); lymphocytic cellular infiltrates (0/10, 2/9, 7/10, 8/10) Kidney: renal tubule degeneration (0/10, 0/10, 0/10, 7/10); renal tubule hypertrophy (0/10, 0/10, 2/10, 5/10) Pituitary gland: pars distalis hypertrophy (0/10, 0/10, 2/9, 6/10)
Neoplastic effects	None	None	None	None
Genetic toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Positive in male and female Tg.AC hemizygous mice		

Summary of the 27- and 43-Week Carcinogenesis and Genetic Toxicology Studies of Sodium Bromate in p53 Haploinsufficient Mice

	Males		Females	
	27 Weeks	43 Weeks	27 Weeks	43 Weeks
Concentrations in water	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L	0, 80, 400, or 800 mg/L
Body weights	Exposed groups similar to the control group	Exposed groups similar to the control group	400 and 800 mg/L groups less than the control group	400 and 800 mg/L groups less than the control group
Survival rates	14/15, 14/15, 14/15, 14/15	9/10, 8/10, 8/10, 9/10	14/15, 15/15, 15/15, 14/15	9/10, 9/10, 10/10, 10/10
Nonneoplastic effects	None	None	None	None
Neoplastic Effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:		Positive in male and female p53 haploinsufficient mice		

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 Report on sodium bromate on September 27, 2005, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

Charlene A. McQueen, Ph.D., Chairperson
College of Pharmacy
University of Arizona
Tucson, AZ

Diane F. Birt, Ph.D., Principal Reviewer
Department of Food Science & Human Nutrition
Iowa State University
Ames, IA

Michael R. Elwell, D.V.M., Ph.D.
Pathology, Drug Safety Evaluation
Pfizer Global Research and Development
Groton, CT

Thomas A. Gasiewicz, Ph.D., Principal Reviewer
Department of Environmental Medicine
Environmental Health Sciences Center
University of Rochester School of Medicine
Rochester, NY

John P. Giesy, Jr., Ph.D., Principal Reviewer
Department of Zoology
Michigan State University
East Lansing, MI

Shuk-Mei Ho, Ph.D.*
Department of Surgery, Division of Urology
University of Massachusetts Medical School
Worcester, MA

Steven M. Roberts, Ph.D.
Center for Environmental & Human Toxicology
University of Florida
Gainesville, FL

Mary Vore, Ph.D.
Graduate Center for Toxicology
University of Kentucky
Lexington, KY

Special Ad Hoc Reviewers

Kenny Crump, Ph.D.
Environ International
Ruston, LA

Prescott Deininger, Ph.D.*
Tulane University Medical Center
New Orleans, LA

Harish Sikka, Ph.D.
Environmental Toxicology and Chemistry Laboratory
State University of New York College at Buffalo
Buffalo, NY

Keith Soper, Ph.D.
Merck Research Laboratories
West Point, PA

Vernon Walker, Ph.D.*
Lovelace Respiratory Institute
Albuquerque, NM

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 27, 2005, the draft Report on the toxicology and carcinogenicity studies of sodium bromate 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 carcinogenicity studies of sodium bromate in genetically modified mice by describing the uses of the chemical, the study design, and the effects of the chemical on survival, body weight, and nonneoplastic lesions in the animals. The proposed conclusions were *no evidence of carcinogenic activity* of sodium bromate in male or female p53 haploinsufficient mice.

Dr. Giesy, the first principal reviewer, said the studies were well designed and performed. He said he would like to see more discussion of the other non-cancer endpoints and possibly some discussion of the perceived utility of the model system.

Dr. Gasiewicz, the second principal reviewer, thought the proposed conclusions were appropriate. He noted that while the chemical was a carcinogen in other rodent models it was not in these models, and he suggested that be highlighted in the discussion. He emphasized the distinction between absolute and relative in descriptions of organ weights, and between statistical and biological significance in descriptions of lesion incidences.

Dr. Birt, the third principal reviewer, asked for better description of the origin of the animals and when in the process of rederiving the mouse strain these were obtained. Overall she agreed with the proposed conclusions.

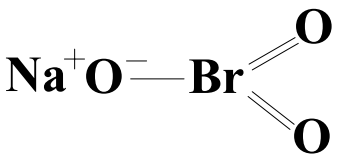
Dr. Hooth noted that while thyroid gland or kidney neoplasms were not seen in these studies as they had been in the traditional 2-year bioassays, those sites were targets of toxicity in these shorter-term studies.

Dr. Roberts noted that different forms of conclusion statements are used for different model strains and that it would be useful to specify how these differ. Dr. C.J. Portier, NIEHS, explained that in the title of the reports the p53 model studies are described as carcinogenesis tests and the Tg.AC models are toxicity studies, with only the former using Levels of Evidence categories for conclusions.

Dr. R.J. Lorentzen, NCTR, suggested that the results of the studies in Tg.AC mice were not inconsistent with other studies performed on brominated compounds that showed kidney toxicity.

Dr. Gasiewicsz moved that the conclusions be accepted as written. Dr. Giesy seconded the motion. The motion was passed unanimously with six votes.

INTRODUCTION



SODIUM BROMATE

CAS No. 7789-38-0

Chemical Formula: $NaBrO_3$ Molecular Weight: 150.9

Synonyms: Bromic acid, sodium salt
Trade names: Dyetone, Neutralizer K-126, Neutralizer K-140, Neutralizer K-938

Chemical and Physical Properties

Sodium bromate is an ionic solid that appears as white granules or a crystalline powder, has no odor or taste, has a melting point of 381° C and a density of 3.4 g/mL, and is soluble in water and insoluble in organic vehicles such as 95% ethanol and acetone (*Merck*, 1983; HSDB, 2003). In the absence of information on sodium bromate, information on potassium bromate will be presented, as both salts produce similar effects and are roughly equivalent in the delivery of bromate ions.

Production, Use, and Human Exposure

Sodium bromate is produced by passing bromine through a solution of sodium carbonate (HSDB, 2003).

Sodium bromate is used as an analytical reagent, in the oxidation of sulfur and vat dyes, and for cleaning boilers. As a mixture with sodium bromide, it is used for dissolving gold from its ores (HSDB, 2003). The cosmetic industry uses sodium bromate and potassium bromate as neutralizers or oxidizers in hair wave preparations. In 1991, the cosmetic industry voluntarily reported to the Food and Drug Administration (FDA) that sodium bromate was present in 61 cosmetic formulations, with concentrations ranging from 10% to 25%; there is no FDA requirement to report this information (*Fed. Regist*., 1992; CIREP, 1994). No information regarding the estimated amount of sodium bromate produced, imported, or exported for the United States or worldwide was found in the literature.

Sodium bromate and potassium bromate are by-products of the water disinfection process. Bromate is one of the disinfection by-products formed during the ozonation of source water containing bromide. Bromide is naturally present in water and the ozonation of waters containing the bromide ion (Br^-) results in the oxidation of Br^- to hypobromous acid (HOBr) and further oxidation of the hypobromite ion (BrO^-) to bromate ($BrO3^-$) (Haag and Holgné, 1983; Glaze, 1986). No information was found reporting the concentrations of bromate in ozonated waters, but laboratory studies indicate that the rate and extent of bromate formation depends on ozone concentration, pH, and contact time (Haag and Holgné, 1983).

Pilot laboratory studies indicated that 60 or 70 µg/L bromate could be observed following treatment of raw water containing 1 or 2 mg/L bromide, respectively, with 2 mg/L ozone (McGuire *et al.*, 1990). The addition of chlorine to water also results in oxidation of bromide to hypobromous acid (Rook, 1974). Once hypobromous acid has been formed, it is possible for bromate to be formed through disproportionation. However, during chlorination, the organic substances in raw water react with the hypobromite ion to produce brominated organic disinfection by-products reducing the concentration of hypobromite that is able to disproportionate to bromate (Bull and Kopfler, 1991). The maximum contaminant level established by the United States Environmental Protection Agency for bromate is 10 µg/L (40 CFR §141.64).

In the workplace, the American Industrial Hygiene Association (1981) requires the use of a dust respirator for airborne concentrations of sodium or potassium bromate in excess of 100 mg/m^3. For the public, the Consumer Product Safety Commission requires that all home permanent wave neutralizing solutions containing greater than 600 mg sodium bromate or 50 mg potassium bromate be enclosed in child-resistant packages (16 CFR §1700.14).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

Bromate appears to be rapidly absorbed from the gastrointestinal tract, at least in part unchanged, following oral administration. Fujii *et al*. (1984) administered a single dose of potassium bromate (50 mg/kg) intragastrically to male Wistar rats. Approximately 35% and 26% of the dose was excreted in the urine as bromate and bromide, respectively, 24 hours after the treatment. The feces contained approximately 1% of the dose. Bromate was not detected in the blood or other tissues after 24 hours. However, bromide was significantly increased in the kidney, pancreas, stomach, small intestine, red blood cells, and plasma, indicating that bromate is distributed to several body tissues and reduced to bromide. The disappearance of potassium bromate from the gastrointestinal tract and plasma and its excretion in urine was investigated by administering 100 mg/kg orally to rats (Fujii *et al*., 1984). Bromate disappeared gradually from the stomach. Maximum concentrations of bromate were observed in the small intestine after 30 minutes and levels were undetectable after 4 hours. Peak plasma and urine concentrations were observed 15 minutes and 1 hour after dosing, respectively. Plasma and urine levels decreased rapidly and were undetectable after 2 and 4 hours, respectively. To determine the dose-response relationship of the excretion of bromate and bromide, a solution of potassium bromate was administered orally to rats at 0, 0.625, 1.25, 2.5, 5.0, 10.0, 20.0, 40.0, 60.0, 80.0, or 100 mg/kg (Fujii *et al*., 1984). No bromate was detected in the urine of rats administered up to 2.5 mg/kg. However at doses higher than 5 mg/kg, dose-related increases in the levels of bromate and bromide excreted in the urine were observed.

Other investigators have reported a much longer half-life of bromide in tissues of male Wistar rats that received 50 µg/g sodium bromate (^{82}Br) in the drinking water *ad libitum* for up to 17 days (Pavelka *et al*., 2000a). Tissues were collected at time intervals of 12 to 396 hours after exposure. Half-lives ranged from 94.3 ± 14.6 hours in thyroid gland to 235.0 ± 88.9 hours in liver. The animals excreted approximately 5% of the administered bromate (^{82}Br) dose 24 hours after treatment and the majority (75%) was excreted in urine (Pavelka *et al*., 2000b).

Absorption of sodium bromate has been studied following dermal application. Sodium bromate, formulated in a cosmetic hair neutralizer, was applied to excised guinea pig skin (0.2 mL of neutralizer containing 16.5 mg of bromate spread over 1.77 cm^2 of skin) for 15 or 30 minutes using glass diffusion cells and 5 mL of buffered solution (CIREP, 1994). The maximum amount of bromine absorbed by the skin after a 30-minute exposure (measured as bromide) was 0.12%. In an *in vivo* study using albino guinea pigs, 0.5 mL of hair neutralizer containing 10.17% sodium bromate was spread over a 5 cm^2 area of shaved skin and left on the skin for 15 minutes before rinsing the area with water (CIREP, 1994). Blood and urine samples were collected for 4 hours after exposure and analyzed for bromate using ion chromatography. No bromate was measured in the blood or urine of treated animals. The limit of detection for the analytical method was 76 ppb.

Small amounts of bromine (1 to 2 ppm) were detected in the adipose tissue of mice, but not of rats, fed bread treated with potassium bromate in a lifetime study (Kurokawa *et al*., 1990).

In vitro studies indicate that liver and kidney homogenates and red blood cells from male Wistar rats degrade bromate to bromide when incubated at 37° C for 30 minutes and that glutathione is probably involved in that degradation (Tanaka *et al*., 1984).

Humans

Lichtenberg *et al.* (1989) described the clinical course of a 2-year-old male (13 kg) with acute bromate poisoning. The child had ingested 1 to 2 ounces of a permanent wave solution containing 10 to 12 g bromate/100 mL. Serum bromide levels peaked 12 hours after ingestion. The amount of bromide recovered from dialysate and urine was 1,850 mg.

Parker and Barr (1951) reported that no bromide or bromine was released following incubation of normal human gastric juice with potassium bromate at 38° C for 3 days. The authors concluded that bromate is absorbed from the stomach unchanged.

TOXICITY

Experimental Animals

The LD_{50} for intraperitoneal injection of sodium bromate was 50 to 200 mg/kg in rats and 140 mg/kg in mice (CIREP, 1994; HSDB, 2003). The oral LD_{50} of potassium bromate in the rat was 200 to 400 mg/kg, and the LD_{100} was 700 mg/kg. A single intragastric dose of potassium bromate was administered to F344 rats, $B6C3F_1$ mice, and Syrian golden hamsters (five/sex per group; Kurokawa *et al*., 1990). Two-thirds of the animals in all species receiving 700 to 900 mg/kg died within 3 hours. The remaining animals receiving these doses died within 48 hours. LD_{50} values were higher for females than for males in all species and ranged from 280 mg/kg for male mice to 495 mg/kg for female rats.

Kurata *et al*. (1992) administered single intragastric doses of 0, 50, 300, 600, and 1,200 mg potassium bromate/kg body weight to 6-week-old male F344/NCr rats. All rats treated with 1,200 mg/kg and four of five rats treated with 600 mg/kg died within 24 hours. Significant increases in relative kidney weights and proximal tubule necrosis were observed in these rats.

The effects of potassium bromate on renal function and morphology were studied in male Wistar rats given a single intraperitoneal injection of 50, 75, or 125 mg/kg (Giri *et al*., 1999). Examination of kidneys revealed a proliferative response and renal damage as was evident by a dose-dependent increase in ornithine decarboxylase activity, increased ^{3}H-thymidine incorporation into DNA, depletion of renal glutathione and glutathione reductase activity, and increased blood urea nitrogen and serum creatinine levels. It was concluded that potassium bromate induces oxidative damage through the generation of reactive oxygen species, which results in renal cell proliferation and renal damage.

The potential effects of sodium bromate on the immune system were evaluated by the National Toxicology Program (VCU, 2000; Guo *et al*., 2001). Sodium bromate was administered to female $B6C3F_1$ mice in drinking water for 28 days at doses of 80, 200, 400, 600, and 800 mg/L. No significant differences from those of the control group were observed in body weights, body weight gains, or the weights of thymus, liver, kidney, or lung of exposed groups. However, animals exposed to sodium bromate had significant increases in absolute (28%) and relative (26%) spleen weights. The erythrocyte counts, hemoglobin, hematocrit, mean cell volume, platelet count, total leukocyte count, and counts of differential leukocytes were unaffected by exposure to sodium bromate. A dose-related increase in reticulocytes was observed following exposure to sodium bromate with the greatest increase (78%) observed at 800 mg/L. Overall, there were no changes in the absolute number of total T cells, $CD4^+CD8^-$ T cells, $CD4^-CD8^+$ T cells, natural killer cells, or macrophages. Exposure to sodium bromate did not affect the percentage of B cells. There was no alteration in IGM antibody-forming cell response, mixed leukocyte reaction, or natural killer cell activity after exposure to sodium bromate. When the activity of peritoneal macrophages, unstimulated or stimulated with IFN-gamma and LPS, was evaluated using the cytotoxic/cytostatic assay of B16F10 tumor cells, the suppressive effect of macrophages on the proliferation of B16F10 tumor cells was decreased after exposure to sodium bromate. Sodium bromate produced minimal toxicological and immunotoxic effects in female $B6C3F_1$ mice.

Accumulation of α2u-globulin and the induction of cell proliferation were examined in kidneys of rats exposed to potassium bromate, potassium bromide, or sodium bromate in the drinking water (Umemura *et al*., 1993). Hyaline droplets observed after exposure to potassium or sodium bromate in male rats were immunostained positive for α2u-globulin. Increases in cell proliferation were found in the proximal tubules of male rats given

potassium or sodium bromate but not potassium bromide after 2, 4, and 8 weeks. Similar changes were not observed in female rats or in the distal tubules of any treated rats.

The subchronic effects of potassium bromate were evaluated by Kurokawa *et al*. (1990). Potassium bromate was administered in the drinking water at concentrations of 0, 150, 300, 600, 1,250, 2,500, 5,000, or 10,000 mg/L to male and female F344 rats (10/sex per group) for 13 weeks. All animals exposed to greater than 1,250 mg/L died within 7 weeks. Significant inhibition of body weight gain was observed in males exposed to 600 or 1,250 mg/L. Significant increases in serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, Na^+, and cholinesterase) were observed in males and females at 600 mg/L. Various-sized droplets and regenerative changes were observed in the renal tubules of treated males.

Male Wistar rats were exposed to 0.04% potassium bromate in the drinking water for up to 15 months (Nakano *et al*., 1989). Body weight gain was significantly inhibited in treated animals. Pyknotic foci were observed in the tubules of the inner medulla of the kidneys at 7 to 11 weeks. Blood urea nitrogen was increased after 15 months.

Groups of 10 male and 10 female $B6C3F_1$ mice were given 250, 500, 1,000, 2,000, or 4,000 mg/L potassium bromate in the drinking water for 10 weeks (Kurokawa *et al*., 1990). Doses greater than 2,000 mg/L were not palatable. No treatment-related deaths were observed at doses less than 1,000 mg/L, and no histopathologic changes were attributed to potassium bromate administration.

The sensitization potential of 10.17% aqueous solution full strength sodium bromate was evaluated using the Buehler method in guinea pigs (CIREP, 1994). Only five of 19 guinea pigs had any signs of sensitization of Grade 1 irritation at 24 hours and only two of five animals had reactions at 24 hours. The authors concluded that the undiluted formulation of sodium bromate was a mild sensitizer.

Humans

Several cases of acute bromate intoxication have been reported in humans following accidental or suicidal ingestion of permanent hair wave neutralizing solution. These products usually contain either 2% potassium bromate or 10% sodium bromate. Bromate intoxication leads to gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea), central nervous system depression, renal failure, and hearing loss. Bromate intoxication has been reported to be lethal (Kitto and Dumars, 1949; Matsumoto *et al*., 1980).

Kidney effects are frequently observed in children and adults following acute exposure with sodium and potassium bromate and include anuria, oliguria, and renal failure (Kitto and Dumars, 1949; Quick *et al*., 1975; Matsumoto *et al*., 1980; Gradus *et al*., 1984; Kutom *et al*., 1990; Watanabe *et al*., 1992). A review of bromate kidney toxicity found that renal failure occurred in 26 of 31 reported cases (Matsumoto *et al*., 1980). Histological examination of renal biopsies from children with renal effects indicated interstitial edema, tubular atrophy and dilation, interstitial fibrosis, and epithelial separation of the proximal tubules (Quick *et al*., 1975; Watanabe *et al*., 1992).

Bromate exposure produces irreversible deafness in children and adults. Quick *et al*. (1975) described a 6-year-old boy who ingested approximately 0.5 grams of 95% pure potassium bromate pellets. The serum bromide level of this patient was 17 mg/100 mL. Gradus *et al*. (1984) described a 17-month-old girl who ingested an unknown amount of permanent wave neutralizer solution containing potassium bromate. Both children developed vomiting, diarrhea, and anuria. Audiographic examinations indicated that the children had severe bilateral hearing loss. Matsumoto *et al*. (1980) reported two cases of women who ingested 10 and 15 grams of potassium bromate, respectively, and lost their hearing within 12 hours of ingestion. A review of bromate ototoxicity by these authors found that deafness occurred in 17 of 20 cases in Japan usually 4 to 16 hours after ingestion.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Experimental Animals

The National Toxicology Program (1996) evaluated the potential reproductive and developmental toxicity of sodium bromate in Sprague-Dawley rats following oral administration in the drinking water. A dose range-finding study was conducted at concentrations of 0, 250, 500, 1,000, and 2,000 mg/L to select concentrations for

a 35-day study. Based on exposure concentration-related body weight decreases and decreased feed and water consumption, the concentrations chosen for the 35-day drinking water study were 0, 25, 80, and 250 mg/L. One group of male rats and two groups of female rats were treated at each exposure level. One group of females was exposed from study day 1 to 34 to test for effects during conception and early gestation. The other group of females was exposed from gestation day 6 to postnatal day 1 to test for effects during late gestation and birth. Females in this group were allowed to litter, and the pups were observed through postnatal day 5. Sodium bromate resulted in no treatment-related findings in body weights, feed consumption, clinical observations, or gross or microscopic changes in the kidney, liver, spleen, testis, or epididymis. There were no changes observed in the reproductive data for the females. There was an exposure concentration-related decrease in epididymal sperm density in treated males, which was statistically significant at 250 mg/L (18%), but there were no effects on male fertility.

Sodium bromate was evaluated for potential reproductive toxicity using the multigeneration, continuous-breeding paradigm (NTP, 2001). Sodium bromate was administered to male and female Sprague-Dawley rats in drinking water at concentrations of 0, 30, 100, and 300 mg/L. Sodium bromate produced general toxicity in male and female Sprague-Dawley rats at 100 and 300 mg/L as noted by chronic progressive nephropathy and hyaline droplets in males and renal cell proliferative changes in females. Sodium bromate was not considered a reproductive toxicant as no treatment-related changes were observed in the reproductive litter data. In males, there was a 16% decrease in sperm density in the F_0 generation. This finding was consistent with a decrease of 18% in sperm density noted in the screening study. In the F_1 generation, the sperm density was still decreased by 8%, but the difference was not statistically significant.

Humans

No reproductive or developmental toxicity studies of sodium bromate or potassium bromate in humans were found in the literature.

CARCINOGENICITY

Experimental Animals

Male and female F344 rats (53/sex per group) were given potassium bromate in drinking water at concentrations of 0, 250, or 500 mg/L for 110 weeks (Kurokawa *et al*., 1982, 1983a). The 500 mg/L concentration was reduced to 400 mg/L during week 60 as a result of a decrease in body weight gain in male rats. The incidences of renal cell tumors (adenomas and adenocarcinomas) in exposed males and females and peritoneal mesotheliomas in exposed males were significantly increased compared with controls. Potassium bromate induced high incidences of renal cell tumors that showed a dose-response relationship in both male and female F344 rats. Renal cell tumors developed in 0% (control), 56% (250 mg/L), and 80% (500 mg/L) of female rats and 6% (control), 60% (250 mg/L), and 88% (500 mg/L) of male rats.

Dose response-studies on the carcinogenicity of potassium bromate were then conducted (Kurokawa *et al*., 1986a). Male F344 rats were given 0, 15, 30, 60, 125, 250, or 500 mg/L potassium bromate in drinking water for 104 weeks. The combined incidence of renal adenomas or adenocarcinomas was significantly increased in a dose-related manner in male rats exposed to 125, 250, or 500 mg/L. The incidences of thyroid gland follicular adenoma or adenocarcinoma (combined) and of peritoneal mesotheliomas were significantly increased in the 500 mg/L group.

To assess the time-course of renal tumor induction, male F344 rats were given 500 mg/L potassium bromate in drinking water for up to 104 weeks (Kurokawa *et al*., 1987a). In one study, administration of potassium bromate was stopped at week 13, 26, 39, 52, or 104, and rats were killed immediately. Renal adenomas were detected as early as 26 weeks. The incidences of renal dysplastic foci, adenomas, and adenomas or adenocarcinomas combined were significantly increased over controls by 52 weeks of treatment. The incidences of thyroid gland follicular adenomas, adenomas or adenocarcinomas (combined), and peritoneal mesotheliomas were significantly increased in rats receiving potassium bromate for 104 weeks. In another study, male F344 rats were given

drinking water containing 500 mg/L potassium bromate for 13, 26, 39, or 52 weeks and maintained on drinking water alone until sacrifice at week 104. The incidences of renal dysplastic foci, adenomas, and adenomas or adenocarcinomas combined in rats exposed for 13 to 52 weeks were equal to or greater than those in rats continuously exposed to potassium bromate for 104 weeks.

Female $B6C3F_1$ mice were exposed to 500 or 1,000 mg/L potassium bromate in drinking water for 78 weeks and thereafter given tap water for 26 weeks (Kurokawa *et al*., 1986b). Mice were killed at week 104. No significant differences in tumor incidences were observed between treated and control groups. In a subsequent study, 750 mg/L potassium bromate was administered orally to male $B6C3F_1$, BDF_1, and CDF_1 mice for 88 weeks. Significant increases in the numbers of small intestine adenomas in CDF_1 mice and liver adenomas in $B6C3F_1$ mice were observed (Kurokawa *et al*., 1990).

More recently, male F344/N rats and $B6C3F_1$ mice were given potassium bromate in drinking water at concentrations of 0, 0.02, 0.1, 0.2, or 0.4 g/L (rats) and 0, 0.08, 0.4, or 0.8 g/L (mice) for up to 100 weeks (DeAngelo *et al*., 1998). For rats, the incidences of renal cell tumors and thyroid gland follicular tumors were significantly increased in the 0.4 g/L group. In addition, the incidences of mesotheliomas were significantly increased in the 0.1, 0.2, and 0.4 g/L groups. For mice, the incidence of renal cell tumors was significantly increased in the 0.08 g/L group, but the higher exposure groups did not exhibit an increased incidence of renal cell tumors when compared to the control groups (control, 0/40; 0.08 g/L, 5/38; 0.4 g/L, 3/41; 0.8 g/L, 1/44). To investigate the time- and dose-dependent development of potassium bromate-induced tumors in male F344 rats, potassium bromate was dissolved in the drinking water at nominal concentrations of 0, 0.02, 0.1, 0.2, and 0.4 g/L and given for 12, 26, 52, 78, or 100 weeks (Wolf *et al*., 1998). Thyroid gland follicular tumors were seen as early as 26 weeks in one rat each from the 0.1 and 0.2 g/L groups. Renal cell tumors and mesotheliomas were seen in the 0.4 g/L group after 52 and 78 weeks of treatment, respectively.

The carcinogenic potential of potassium bromate was also studied in Syrian golden hamsters (Takamura *et al*., 1985). Groups of 20 male hamsters received 125, 250, 500, or 2,000 mg/L potassium bromate in drinking water for 89 weeks. Renal cell tumors developed in the three highest exposure groups but the incidences were not statistically significant. Because this species rarely develops spontaneous renal tumors, the authors concluded that potassium bromate has the potential to induce renal tumors in the golden hamster.

Potassium bromate was tested in two-stage carcinogenesis assays to determine whether it was able to initiate or promote carcinogenesis. Male F344 rats were given 500 or 1,000 mg/L *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) in drinking water as an initiator for 2 weeks and then given 500 mg/L potassium bromate in drinking water as a promoter for 24 weeks. All animals were killed during week 26. Average numbers of dysplastic foci and renal cell tumors were significantly increased in male rats given potassium bromate after initiation with EHEN. The authors concluded that potassium bromate was able to initiate and promote renal carcinogenesis (Kurokawa *et al*., 1983b). In contrast, initiating activity was not observed when male F344/NCr rats (29 or 39 per group) were given a single intragastric dose of 300 mg/kg potassium bromate (Kurata *et al*., 1992). Two weeks after potassium bromate treatment, the animals were maintained on a basal diet or a diet containing 4,000 ppm sodium barbital as a promoting agent. A single oral dose of potassium bromate did not initiate renal tumors within a 104-week observation period.

Dose-response studies were conducted to investigate the enhancing effect of potassium bromate on renal carcinogenesis initiated by EHEN (Kurokawa *et al*., 1985). EHEN (500 ppm) was given to 6-week-old male F344 rats in drinking water for 2 weeks followed by 15, 30, 60, 120, 250, or 500 mg/L potassium bromate in drinking water for 24 weeks. Additional groups initiated with EHEN were given potassium bromide in drinking water at concentrations of 350 or 1,750 mg/L for 24 weeks. The numbers of dysplastic renal foci per cm^2 were significantly increased in an exposure concentration-related manner from 30 mg/L to 500 mg/L. The numbers of renal cell tumors per cm^2 were significantly increased in the 500 mg/L group. It was concluded that the threshold concentration of potassium bromate for the enhancement of renal carcinogenesis was between 15 and 30 mg/L. No enhancement of renal carcinogenesis was observed with potassium bromide.

Potassium bromate was tested for promoting and complete carcinogenic activities in skin carcinogenesis studies using Sencar mice (Kurokawa *et al*., 1984). Potassium bromate (8 mg in 0.2 mL of acetone) was applied to the dorsal skin of mice twice a week for

51 weeks to determine if it was a complete carcinogen. In the promotion studies, mice received a single topical application of 7,12-dimethylbenz(a)anthracene (20 nmol in 0.2 mL acetone) and potassium bromate (8 mg in 0.2 mL of acetone) was applied to initiated skin twice a week for 51 weeks. No skin tumors developed in either bromate-treated group. The authors concluded that potassium bromate is not a skin carcinogen or a promoter of skin cancer in Sencar mice.

The carcinogenicity of potassium bromate was tested in newborn F344 rats and ICR mice (Matsushima *et al*., 1986). Male and female rats and mice (24 hours old) were given single subcutaneous injections of potassium bromate or four weekly injections until weaning for total doses in the range of 12.5 to 800 mg/kg body weight. Rats were sacrificed at 82 weeks and mice were sacrificed at 78 weeks. No significant differences in the incidences of tumors in male or female rats or mice were observed.

Carcinogenicity studies were conducted in male and female Wistar rats and Theiller strain mice by feeding animals diets containing bread made from flour treated with 0, 50, or 75 ppm potassium bromate for 104 and 80 weeks, respectively (Fisher *et al*., 1979; Ginocchio *et al*., 1979). No carcinogenic effects were produced in rats or mice.

Humans

No epidemiology studies of sodium bromate or potassium bromate in humans were found in the literature.

Genetic Toxicity

There is little published mutagenicity data for sodium bromate. In an abstract that presented a brief description of test results, but no data, Eckhardt *et al*. (1982) reported negative results with sodium bromate in a *Salmonella typhimurium* mutagenicity assay and a sex-linked recessive lethal assay in male *Drosophila melanogaster*. However, these same authors reported dose-dependent increases in micronuclei in mouse bone marrow cells following exposure to sodium bromate (no experimental details were provided).

There is a more extensive literature describing the mutagenic activity of potassium bromate, including reports of positive results in *Salmonella* mutagenicity assays using base-pair substitution strains TA100, TA102, and TA104 in the presence of exogenous metabolic activation enzymes (Ishidate *et al*., 1984; Kurokawa *et al*., 1990) or the frame-shift strain TA97, with and without S9 (Zeiger *et al*., 1992), as well as induction of chromosomal aberrations, micronuclei, DNA strand breaks, oxidative DNA base damage, and HPRT gene mutations in cultured Chinese hamster fibroblast cells (Ishidate *et al*., 1984; Speit *et al*., 1999). Acute *in vivo* studies with potassium bromate demonstrated dose-related increases in the frequencies of chromosomally aberrant metaphases in bone marrow cells of rats treated by gavage or intraperitoneal injection (Fujie *et al*., 1988). In addition, potassium bromate was reported to induce micronuclei in polychromatic erythrocytes of rats treated by intraperitoneal injection (Sai *et al*., 1992a) and of mice treated by gavage (Hayashi *et al*., 1988, 1989; Nakajima *et al*., 1989) or intraperitoneal injection (Hayashi *et al*., 1988; Awogi *et al*., 1992). It has been proposed that the mechanism for bromate genotoxicity in these test systems involves metabolic generation of reactive intermediates (Kurokawa *et al*., 1990) in the form of bromine radicals (Ballmaier and Epe, 1995; Speit *et al*., 1999) rather than reactive oxygen species.

Background on Genetically Altered Mice

Mutation and/or deletions of tumor suppressor genes or activation of protooncogenes can disrupt cell function and predispose an animal to cancer. In the current studies, two genetically altered mouse models with either a loss of heterozygosity in a critical cancer gene (Trp53) or a gain of oncogene function (Ha *ras*) were used to determine how these animals would respond to sodium bromate exposure. These mouse models are susceptible to the rapid development of cancer. The Tg.AC hemizygous and p53 haploinsufficient mice are being evaluated by the National Institute of Environmental Health Sciences (NIEHS) and the NTP as models for identifying chemical toxicity and/or chemical carcinogenic processes (Tennant *et al*., 1996; Pritchard *et al.*, 2003).

FVB/N-TgN(v-Ha-ras)Led (Tg.AC) Hemizygous Mouse Model

Tg.AC mice are hemizygous for a mutant v-Ha-*ras* transgene. The Tg.AC hemizygous mouse (on an FVB/N background) was developed by Leder *et al.* (1990) by introduction via pronuclear injection of a tripartite transgene composed of the promotor of the mouse

embryonic zeta-globin gene, through the v-Ha-*ras* coding sequence, with point mutations in codons 12 and 59, and an SV40 polyadenylation sequence. Because the inducible zeta-globin promoter drives the expression of a mutated v-Ha-*ras* oncogene, the Tg/AC mouse is regarded as a genetically initiated model.

The Tg.AC transgenic mouse model has been evaluated as a reporter phenotype (skin papillomas) in response to either genotoxic or nongenotoxic carcinogens, including tumor promoters (Spalding *et al.,* 1993, 1999; Tennant *et al.,* 1999). With the exception of bone marrow, constitutive expression of the transgene cannot be detected in adult tissues. The transgene is transcriptionally silent until activated by certain treatments including full-thickness wounding, ultraviolet irradiation, or exposure to some chemicals (Cannon *et al.,* 1997; Trempus *et al.,* 1998). The Tg.AC hemizygous mouse develops a high incidence of skin papillomas in response to topical application of 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA), and TPA has been used as a positive control in NIEHS Tg.AC mouse studies (Spalding *et al.,* 1993). TPA has been used a a positive control in NIEHS Tg.AC mouse studies to confirm the mice are responsive to carcinogens because it has been found that a subset of Tg.AC mice may revert and become nonresponsive to a tumor promoter (Honchel *et al*., 2001). Point mutations in the Ha-*ras* gene are believed to be early events in the induction of skin papillomas and malignancies. Topical application of carcinogens to the shaved dorsal surface of Tg.AC mice induces epidermal squamous cell papillomas or carcinomas, a reporter phenotype that defines the activity of the chemical. The oral route of administration can also generate tumor responses in the skin of Tg.AC mice and lead to squamous cell papillomas and/or carcinomas of the forestomach. To date, the appearance of either spontaneous or induced tumors has been shown to involve transgene expression. However, the mechanism of response by the Tg.AC model to chemical carcinogens is not yet understood.

In NIEHS studies, mice are exposed beginning at 2 months of age for a total of 6 to 9 months. Cutaneous papillomas at various sites have been reported at 10% and 7% incidence in 33-week-old control male and female Tg.AC mice, respectively (Mahler *et al.,*1998). Cutaneous papillomas occurring at sites such as the lip, pinnae, prepuce, and vulva suggest a possible relationship to grooming and chronic irritation. Up to 32% of Tg.AC homozygous and heterozygous male or female mice develop odontogenic tumors as early as 33 weeks (Wright *et al.,* 1995; Mahler *et al.,* 1998). A number of different tumor types occur in untreated Tg.AC hemizygous mice at an incidence of greater than 3% including odontogenic tumors, forestomach papillomas, cutaneous papillomas, alveolar/bronchiolar adenomas, salivary gland duct carcinomas, and erythroleukemia (Mahler *et al.,*1998). In the FVB mouse (the background strain for the Tg.AC hemizygous mouse), alveolar/bronchiolar neoplasms occur at 14 months of age (Mahler *et al.,* 1996).

The Tg.AC hemizygous mouse model was used in the current report for the studies of sodium bromate because this model has been reported to detect both nongenotoxic and genotoxic carcinogens (Spalding *et al.,* 1993; Tennant *et al.,* 1995*,* 1996; Pritchard *et al.,* 2003).

B6.129-Trp53^{tm1Brd} (N5) Haploinsufficient Mouse Model

The heterozygous B6.129-Trp53 (N12)$^{tm1Brd(+/-)}$ mouse (on a B6.129S7 background) was developed by Donehower *et al.* (1992). A null mutation was introduced into one p53 allele by homologous recombination in murine embryonic stem cells. Insertion of a neo cassette resulted in deletion of a 450-base pair gene fragment containing 106 nucleotides of exon 5 and approximately 350 nucleotides of intron 4.

Trp53, a nuclear protein, plays an essential role in the regulation of the cell cycle, specifically in the transition from G_0 to G_1, as well as G_2 to M, and the spindle apparatus. The p53 protein has a short half-life and exists at a very low concentration under normal cell physiological conditions. However, in DNA damaged cells that are able to replicate, p53 is expressed in high amounts with a significant increase in half-life due to posttranslational modification (phosphorylation or acetylation). Mutation in p53 may also increase the protein half-life and alter the functions that may contribute to transformation and development of the malignant phenotype. p53 is a DNA-binding protein containing DNA-binding, oligomerization, and transcription activation domains. Many amino acid residues in different p53 domains may be phosphorylated or acetylated, which may determine specific p53 functions. It is postulated to bind as a tetramer to a p53-binding site and activate expression of downstream genes that inhibit growth and/or invasion or promote apoptosis, functioning as a tumor suppressor. This protein is critical to tumor suppression in humans and rodents. Mutants of p53 that fail to bind the consensus DNA binding site, and hence are unable to function as tumor suppressors, frequently occur in human

cancers. Alterations of the Tp53 gene occur not only as somatic mutations in human malignancies, but also as germ line mutations in some cancer-prone families with Li-Fraumeni syndrome.

The mouse heterozygous for a p53 null allele (+/–) has only a single functional wild-type p53 allele which provides a target for mutagens. The p53 tumor suppressor gene is one of the most common sites for mutations and gene alterations in human cancer (Harris, 1996a,b,c)

Heterozygous $p53^{(+/-)}$ mice develop normally, and like humans and other mammals, develop cancer (primarily lymphomas or sarcomas) with age, but often with decreased latency.

STUDY RATIONALE

Sodium bromate was nominated for toxicity and carcinogenicity studies in genetically modified mouse models by the United States Environmental Protection Agency and the National Institute of Environmental Health Sciences. Sodium bromate is a drinking water disinfection by-product formed during the ozonation of source water containing bromide. The objective of this study was to determine whether the use of genetically modified mice could reduce study length while being more effective at determining potential hazards of drinking water disinfection by-products compared to traditional rodent bioassays. Given the hundreds of potentially hazardous disinfection by-products (Bull *et al*., 1995), usually at very low concentrations and occurring as mixtures, a more efficient process for determining safety of chemicals and chemical mixtures found in finished drinking water is needed.

This report focuses on Tg.AC hemizygous and p53 haploinsufficient strains that were exposed to sodium bromate in the drinking water for up to 43 weeks. The Tg.AC hemizygous mouse strain was also exposed to sodium bromate by the dermal route, which if predictive, could prove to be the most efficient screening procedure for drinking water mixtures.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

Sodium Bromate

Sodium bromate was obtained from Fisher Scientific (Fairlawn, NJ) in one lot (946272A) that was used in the 26- and 39-week dermal studies and in the 27- and 43-week drinking water studies. Identity and purity analyses were conducted by the analytical chemistry laboratories, Research Triangle Institute (RTI) (Research Triangle Park, NC) and Battelle Memorial Institute (Columbus, OH), and by the study laboratory, Battelle Columbus Operations (Columbus, OH) (Appendix G). Reports on analyses performed in support of the sodium bromate studies are on file at the National Institute of Environmental Health Sciences.

Lot 946272A, a white crystalline powder, was identified as sodium bromate by infrared (IR) spectroscopy, elemental analysis, and inductively coupled plasma emission (ICP) spectrometry. The purity of lot 946272A was determined using ion chromatography (IC) and iodometric titration of bromate ions. IC indicated one major peak and no impurities with relative areas greater than 0.1% and purities of 101.2% relative to a frozen reference standard and 97% based on bromate anion recovery. Iodometric titration indicated a purity of approximately 99%. The overall purity of lot 946272A was determined to be 99% or greater.

To ensure stability, the bulk chemical was stored at room temperature, protected from light. Stability was monitored during the 26-, 27-, 39-, and 43-week studies using IC. No degradation of the bulk chemical was detected.

12-*O*-Tetradecanoylphorbol-13-acetate

12-*O*-tetradecanoylphorbol-13-acetate (TPA) was obtained from Sigma-Aldrich Chemical Company (St. Louis, MO) in one lot (48H1178) that was used for positive control Tg.AC hemizygous mice in the 26- and 27-week studies.

Lot 48H1178, a white crystalline powder, was identified as 12-*O*-tetradecanoylphorbol-13-acetate using IR and proton nuclear magnetic resonance spectrometry. The purity of lot 48H1178 was determined using high performance liquid chromatography. The overall purity of lot 48H1178 was determined to be greater than 99%.

Ethanol

USP-grade 95% ethanol was obtained from Spectrum Chemicals and Laboratory Products (Gardena, CA) in one lot (NK0283) that was used in the 26- and 39-week dermal studies.

Lot NK0283, a clear liquid, was identified as ethanol using IR spectroscopy. The purity of lot NK0283 was determined using gas chromatography (GC). GC indicated one major peak and no impurities with areas greater than or equal to 0.1% of the major peak. The overall purity of lot NK0283 was determined to be greater than 99%.

The purity of the bulk chemical was periodically monitored during the studies using GC. No degradation of the ethanol was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dermal Studies

The dose formulations were prepared every 4 to 5 weeks by mixing sodium bromate and 40% USP-grade 95% ethanol/60% deionized water to give the required concentrations (Table G1). The dose formulations were stored at room temperature in clear glass bottles for up to 35 days. A positive control dose formulation of TPA was prepared twice during the studies by adding the appropriate amount of TPA to acetone; the formulations were stored at approximately 5° C in amber glass bottles for up to 6 months.

Stability studies of a 5.67 mg/mL dose formulation were conducted using IC. Stability was confirmed for at least 35 days for dose formulations stored in 100 mL glass bottles at temperatures up to ambient, for at least 3 hours for dose formulations stored in capped, partially filled

clear glass scintillation vials, and for at least 24 hours for dose formulations stored exposed to light and air at 25° C to 30° C followed by resolubilization in 40% USP-grade 95% ethanol/60% deionized water.

Periodic analyses of the dose formulations of sodium bromate were conducted using IC. During the 26- and 39-week studies, dose formulations were analyzed four times. All 12 of the dose formulations used for Tg.AC hemizygous mice were within 10% of the target concentrations (Table G2).

Drinking Water Studies

The dose formulations were prepared every 2 to 5 weeks by adding a specified amount of sodium bromate to tap water (Table G1). The dose formulations were stored for up to 35 days at room temperature in the NALGENE® tanks in which they were mixed. A positive control dose formulation of TPA was prepared and stored as described for the dermal studies.

Stability studies of a 5.67 mg/mL dose formulation were conducted by the analytical chemistry laboratory using IC. Stability was confirmed for at least 35 days for dose formulations stored in 100 mL glass bottles at temperatures up to ambient, and for at least 7 days in partially filled 500 mL clear glass drinking bottles.

Periodic analyses of the dose formulations of sodium bromate were conducted by the study laboratory using IC. During the 27- and 43-week studies, the dose formulations were analyzed four times. All 13 of the dose formulations used for Tg.AC hemizygous and p53 haploinsufficient mice were within 10% of the target concentrations (Table G3). No sodium bromate was found in control formulations above a method detection limit of 0.45 mg/L.

Study Designs

Dermal Studies

Groups of 15 male and 15 female Tg.AC hemizygous mice received dermal applications of 0, 64, 128, or 256 mg/kg sodium bromate in ethanol/water (40%/60%) 5 days per week for 26 weeks; the dosing volume was 3.3 mL/kg. Groups of 10 male and 10 female Tg.AC hemizygous mice were administered the same doses for 39 weeks. Vehicle control mice were administered the ethanol/water vehicle only. Doses were applied to the clipped dorsal skin from the mid-back to the interscapular area. A high dose of 800 mg/L was selected for the drinking water studies based on a carcinogenicity study of potassium bromate administered in the drinking water to mice (DeAngelo *et al*., 1998).

Drinking Water Studies

Groups of 15 male and 15 female Tg.AC hemizygous and p53 haploinsufficient mice were exposed to drinking water containing 0, 80, 400, or 800 mg/L sodium bromate for 27 weeks. Groups of 10 male and 10 female Tg.AC hemizygous and p53 haploinsufficient mice were exposed to the same concentrations for 43 weeks. A 14-day range finding study was conducted in FVB/N mice to determine doses for the 26-week study in Tg.AC mice (data not shown). The doses selected were 0, 16, 32, 64, 128, and 256 mg/kg, which were comparable on a weight basis to the concentrations used in the drinking water studies. Because there was no toxicity in the dose range finding study, concentrations of 64, 128, and 256 mg/kg were selected for the 26-week Tg.AC dermal study.

Positive Control Mice

Since it has been found that a subset of Tg.AC mice may revert and become nonresponsive to a tumor promoter (Honchel *et al.*, 2001), positive control groups of 15 male and 15 female Tg.AC hemizygous mice were administered 1.25 µg TPA in 100 µL acetone (12.5 µg TPA/L solution) dermally, three times per week for 26 to 27 weeks to confirm that the mice used in these dermal and drinking water studies of sodium bromate were responsive to carcinogens. The TPA solution was applied to the clipped dorsal skin from the mid-back to the interscapular area. Positive control mice were removed from study after the appearance of 20 or more skin papillomas and discarded.

Source and Specification of Animals

Male and female FVB/N-TgN(v-Ha-*ras*) (Tg.AC) hemizygous (Tg.AC hemizygous) and B6.129-*Trp53*^{tm1Brd} (N5) haploinsufficient (p53 haploinsufficient) mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 26-, 27-, 39-, and 43-week studies. Tg.AC hemizygous mice were quarantined for 16 days before the beginning of the dermal studies and for 13 days before the beginning of the drinking water studies; p53 haploinsufficient mice were quarantined for 14 days before the beginning of the drinking water studies. Five male and five female mice per strain were randomly selected for parasite evaluation and gross observation of disease. Tg.AC hemizygous mice were 6 weeks old and p53 haploinsufficient mice

were 6 to 8 weeks old at the beginning of the studies. Blood samples were collected from five male and five female sentinel mice per strain and study group at 4 and 26 weeks, from five male and five female mice from the highest surviving groups at 39 or 43 weeks, and from moribund mice in the 43-week drinking water studies after June 5, 2000. The sera were analyzed for antibody titers to rodent viruses (Boorman *et al*., 1986; Rao *et al*., 1989a,b). All results were negative.

Animal Maintenance

Mice were housed individually and feed and water were available *ad libitum*. Water consumption was measured weekly by cage during the drinking water studies. Cages and racks were rotated every two weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings and body weights were recorded postdosing on day 1 (dermal studies), initially (drinking water studies), weekly, and at the end of the studies.

In-life observations of papilloma formation on the skin were recorded weekly using the Toxicology Data Management System (TDMS). A papilloma was initially recorded as a mass. The observation "papilloma" was not entered into TDMS for a given animal until the first-observed mass was documented for 3 consecutive weeks. At the third observation, the mass (wart-like in appearance) was entered as a papilloma. Any new mass(es) appearing after the 3-week confirmation period for a given animal at a different site was entered into TDMS first as a mass until the third week, when it was entered as a papilloma. In a few instances, a papilloma that had been previously observed was missing, and therefore not recorded. Reappearance of a mass at a later time was entered into TDMS as a mass until the third observation week, when it was called a papilloma.

At the end of the 26- and 27-week studies, blood was collected from the retroorbital sinus of all mice except the positive control groups for hematology analyses. The mice were anesthetized with a mixture of carbon dioxide and oxygen. Samples for hematology analysis were placed in microcollection tubes (Sarstedt, Inc., Nümbrecht, Germany) coated with potassium EDTA. Hematocrit; erythrocyte, platelet, and leukocyte counts; mean cell hemoglobin; and mean cell hemoglobin concentration were determined with a Cell-Dyn® hematology analyzer (Abbott Diagnostics, Santa Clara, CA).

Hemoglobin concentrations were determined photometrically using a cyanmethemoglobin procedure. Differential leukocyte counts were determined microscopically from blood smears stained with a modified Wright-Giemsa stain. A Miller Disc was used to determine reticulocyte counts from smears prepared with blood stained with new methylene blue. Mean cell volumes were determined from average red blood cell impedance pulse heights. The parameters measured are listed in Table 1.

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

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 39- and 43-week studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney and liver of Tg.AC hemizygous and p53 haploinsufficient mice and the pituitary gland, testis, and thyroid gland of Tg.AC hemizygous mice.

For the 39- and 43-week studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney and liver of Tg.AC hemizygous and p53 haploinsufficient mice and the pituitary gland, testis, and thyroid gland of

Tg.AC hemizygous mice. The quality assessment report and the reviewed slides for the 39- and 43-week studies were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

The 26- and 27-week studies had not undergone a quality assessment review prior to completion of the pathology review for the 39- and 43-week studies. For these studies, a quality assessment pathologist evaluated all tumor diagnoses from all animals and all potential target organs (both genders, both strains, both routes of administration) which included the lung, thyroid, adrenal cortex, kidney, forestomach, liver, thymus, and skin, using terminology and diagnostic criteria defined by the Pathology Working Group for the 39- and 43-week studies in order to maintain diagnostic consistency between the studies. The quality assessment pathologist and two NTP pathologists met to review selected examples of lesions related to chemical administration, and to address any disagreements in the diagnoses made by the laboratory and quality assessment pathologists. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, the quality assessment pathologist, and the NTP pathologists.

TABLE 1
Experimental Design and Materials and Methods in the Dermal and Drinking Water Studies of Sodium Bromate

Dermal Studies	Drinking Water Studies
Study Laboratory Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)
Strain and Species FVB/N-TgN(v-Ha-*ras*) (Tg.AC) hemizygous mice	FVB/N-TgN(v-Ha-*ras*) (Tg.AC) hemizygous mice B6.129-*Trp53*^{tm1Brd} (N5) haploinsufficient mice
Animal Source Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies 16 days	Tg.AC mice: 13 days p53 mice: 14 days
Average Age When Studies Began 6 weeks	Tg.AC mice: 6 weeks p53 mice: 6 to 8 weeks
Date of First Dose or Exposure October 29, 1999	Tg.AC mice: September 28, 1999 p53 mice: September 29, 1999
Duration of Dosing or Exposure 26 or 39 weeks	27 or 43 weeks
Date of Last Dose or Exposure April 25 (males) or 26 (females), 2000 (26-week study) July 25, 2000 (39-week study)	Tg.AC male mice: March 28, 2000 (27-week study) Tg.AC female mice: March 29, 2000 (27-week study) Tg.AC mice: July 18, 2000 (43-week study) p53 male mice: March 30, 2000 (27-week study) p53 female mice: March 31, 2000 (27-week study) p53 mice: July 19, 2000 (43-week study)
Necropsy Dates April 26 (males) or 27 (females), 2000 (26-week study) July 26, 2000 (39-week study)	Tg.AC male mice: March 28, 2000 (27-week study) Tg.AC female mice: March 29, 2000 (27-week study) Tg.AC mice: July 18, 2000 (43-week study) p53 male mice: March 30, 2000 (27-week study) p53 female mice: March 31, 2000 (27-week study) p53 mice: July 19, 2000 (43-week study)
Average Age at Necropsy 32 weeks (26-week study) 45 weeks (39-week study)	Tg.AC mice: 32 weeks (27-week study) Tg.AC mice: 48 weeks (43-week study) p53 mice: 32 to 34 weeks (27-week study) p53 mice: 48 to 50 weeks (43-week study)
Size of Study Groups 15 males and 15 females (26-week study) 10 males and 10 females (39-week study)	15 males and 15 females (27-week study) 10 males and 10 females (43-week study)
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as dermal studies

TABLE 1
Experimental Design and Materials and Methods in the Dermal and Drinking Water Studies of Sodium Bromate

Dermal Studies	Drinking Water Studies
Animals per Cage	
1	1
Method of Animal Identification	
Tail tattoo	Tail tattoo
Diet	
NTP-2000 irradiated pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed weekly	Same as dermal studies
Water	
Tap water (City of Columbus municipal supply) via automated watering system (Edstrom Industries, Waterford, WI)	Tap water (City of Columbus municipal supply) via amber glass water bottles with teflon lined septa (Supelco, Bellefonte, PA) and stainless steel sipper tubes (Ancare, Bellmore, NY), available *ad libitum*, changed at least weekly
Cages	
Solid-bottom polycarbonate (Lab Products, Seaford, DE), changed weekly	Same as dermal studies
Bedding	
Irradiated hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ), changed twice weekly	Same as dermal studies
Rack Filters	
Spun bonded polyester (Snow Filtration Company, Cincinnati, OH), changed every 2 weeks	Same as dermal studies
Racks	
Stainless steel (Lab Products, Inc., Seaford, DE), changed every 2 weeks	Same as dermal studies
Animal Room Environment	
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 13 to 13.1/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Room air changes: 12 to 12.2/hour
Dose or Exposure Concentrations	
0, 64, 128, or 256 mg/kg in ethanol/water (40%/60%) (dosing volume 3.3 mL/kg) or 1.25 µg TPA in 100 µL acetone (positive controls)	0, 80, 400, or 800 mg/L in drinking water, available *ad libitum* or 1.25 µg TPA in 100 µL acetone (positive controls)
Type and Frequency of Observation	
Observed twice daily and clinical findings recorded postdosing on day 1, weekly, and prior to necropsy. Animals were weighed initially, weekly, and at the end of the studies.	Observed twice daily and clinical findings recorded on day 1, weekly, and prior to necropsy. Water consumption was recorded weekly by cage. Animals were weighed initially, weekly, and at the end of the studies.
Method of Sacrifice	
Carbon dioxide asphyxiation	Same as dermal studies

TABLE 1
Experimental Design and Materials and Methods in the Dermal and Drinking Water Studies of Sodium Bromate

Dermal Studies	Drinking Water Studies
Necropsy	
Necropsies were performed on all mice except positive controls. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all mice except positive controls. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.
Clinical Pathology	
Blood was collected from the retroorbital sinus of all mice except positive controls at the end of the 26-week study for hematology. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials	Blood was collected from the retroorbital sinus of all mice except positive controls at the end of the 27-week studies for hematology. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials
Histopathology	
Histopathology was performed on all mice except positive controls. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, large intestine (cecum, colon), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, ovary, pituitary gland, skin, spleen, stomach (forestomach), testis (with epididymis), thymus, thyroid gland, and uterus.	Histopathology was performed on all mice except positive controls. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, large intestine (cecum, colon), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), ovary, pituitary gland, spleen, stomach (forestomach), testis (with epididymis), thymus, thyroid gland, and uterus.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). 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 and Analysis of Lesion Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Appendixes A, B, and C as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. The Fisher exact test (Gart *et al.*, 1979), a procedure based on the overall proportion of affected animals, was used to determine significance.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed or exposed and control groups in the analysis of continuous variables. Organ and body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology data, which has typically skewed distributions, was 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 (1951) 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).

Quality Assurance Methods

The 26-, 27-, 39-, and 43-week studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from these 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 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 Report.

Genetic Toxicology

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 26- and 27-week studies, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of up to 15 animals per group. In addition, the percentage of polychromatic erythrocytes (PCEs) in a population of 1,000 erythrocytes was determined as a measure of bone marrow toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over dose or exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed or exposed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dosed or exposed group is less than or equal to 0.025 divided by the number of dosed or exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 26- and 27-week studies were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects. The percentage of polychromatic erythrocytes data were analyzed by an analysis of variance (ANOVA) test based on individual animal data.

Evaluation Protocol

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

RESULTS

26-WEEK DERMAL STUDY IN Tg.AC HEMIZYGOUS MICE

Positive Control Tg.AC Hemizygous Mice

12-*O*-tetradecanoylphorbol-13-acetate (TPA) (1.25 µg) was dermally administered to groups of 15 male and 15 female Tg.AC hemizygous mice three times weekly for 26 weeks. Papillomas were first observed in week 8; all mice developed more than 20 papillomas each at the site of application (data not shown). This is consistent with historical rates found in other studies (Tennant *et al.*, 2001).

Survival

Estimates of 26-week survival probabilities for male and female mice are shown in Table 2. Survival of all dosed groups was similar to that of the vehicle control groups.

TABLE 2
Survival of Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
Animals initially in study	15	15	15	15
Moribund	2	1	0	0
Natural deaths	1	3	2	0
Animals surviving to study termination	12	11	13	15
Percent probability of survival at end of study[a]	80	73	87	100
Mean survival (days)[b]	163	162	171	181
Survival analysis[c]	P=0.101N	P=0.987	P=0.961N	P=0.224N
Female				
Animals initially in study	15	15	15	15
Moribund	2	4	1	3
Natural deaths	2	1	3	1
Animals surviving to study termination	11	10	11	11
Percent probability of survival at end of study	73	67	73	73
Mean survival (days)	169	157	169	160
Survival analysis	P=1.000N	P=0.923	P=1.000	P=1.000

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dose group is indicated by **N**.

Body Weights and Clinical Findings

Mean body weights of 256 mg/kg male mice were less than those of the vehicle controls during the last 3 weeks of the study; body weights of 64 and 128 mg/kg males and all dose groups of females were similar to those of the vehicle controls throughout the study (Figure 1 and Tables 3 and 4). Treatment-related clinical findings included increased observed papillomas in all dosed groups of males (vehicle control, 1/15; 64 mg/kg, 4/15; 128 mg/kg, 5/15; 256 mg/kg, 5/15) compared to the vehicle control group.

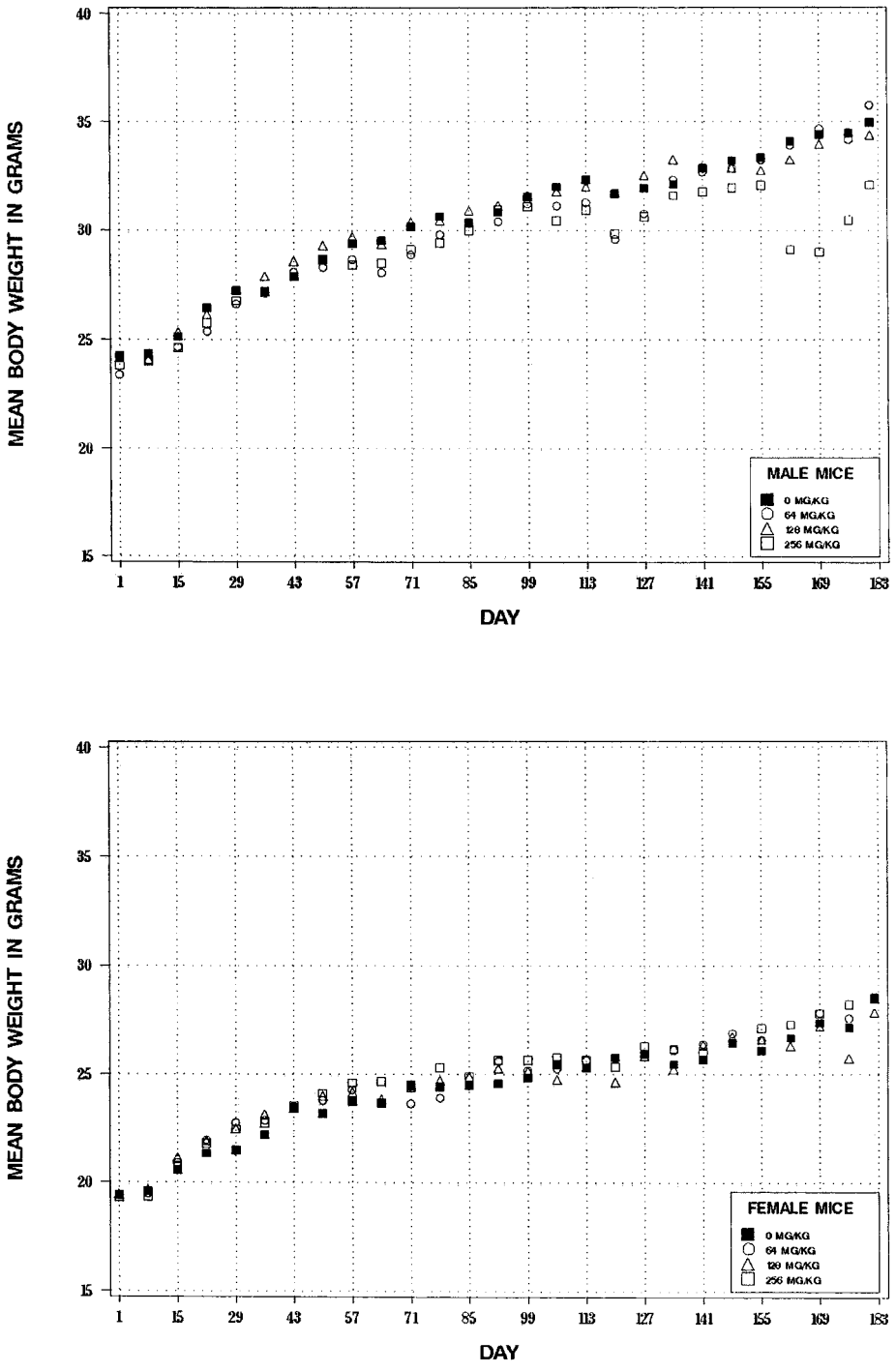


FIGURE 1
Growth Curves for Male and Female Tg.AC Hemizygous Mice Administered Sodium Bromate Dermally for 26 Weeks

TABLE 3
Mean Body Weights and Survival of Male Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

Weeks on Study	Vehicle Control		64 mg/kg			128 mg/kg			256 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.2	15	23.4	97	15	24.2	100	15	23.8	98	15
2	24.4	15	24.0	98	15	24.1	99	15	24.0	98	15
3	25.1	15	24.6	98	15	25.3	101	15	24.6	98	15
4	26.4	15	25.4	96	15	26.1	99	15	25.8	98	15
5	27.2	15	26.6	98	15	27.3	100	15	26.8	99	15
6	27.2	15	27.1	100	15	27.9	103	15	27.1	100	15
7	27.9	14	28.1	101	15	28.6	103	15	27.8	100	15
8	28.7	14	28.3	99	14	29.3	102	15	28.6	100	15
9	29.4	14	28.6	97	14	29.7	101	15	28.4	97	15
10	29.5	14	28.0	95	14	29.3	99	15	28.5	97	15
11	30.2	14	28.9	96	14	30.4	101	14	29.1	96	15
12	30.6	14	29.8	97	13	30.5	100	14	29.4	96	15
13	30.4	13	30.3	100	13	30.9	102	14	30.0	99	15
14	30.8	13	30.4	99	13	31.1	101	14	30.9	100	15
15	31.5	13	31.2	99	13	31.6	100	14	31.1	99	15
16	32.0	13	31.1	97	13	31.8	99	14	30.4	95	15
17	32.3	13	31.3	97	13	32.0	99	14	30.9	96	15
18	31.7	13	29.6	93	13	31.8	100	14	29.8	94	15
19	32.0	13	30.8	96	13	32.5	102	14	30.6	96	15
20	32.1	13	32.3	101	13	33.3	104	14	31.6	98	15
21	32.8	13	32.7	100	12	32.9	100	14	31.8	97	15
22	33.2	12	32.8	99	12	32.9	99	13	31.9	96	15
23	33.3	12	33.2	100	12	32.7	98	13	32.1	96	15
24	34.1	12	33.9	99	12	33.2	97	13	29.1	85	15
25	34.4	12	34.7	101	12	34.0	99	13	29.0	84	15
26	34.5	12	34.2	99	11	34.6	100	13	30.5	88	15
Mean for weeks											
1-13	27.8		27.2	98		28.0	101		27.2	98	
14-26	32.7		32.2	98		32.6	100		30.7	94	

TABLE 4
Mean Body Weights and Survival of Female Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

Weeks on Study	Vehicle Control		64 mg/kg			128 mg/kg			256 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.4	15	19.4	100	15	19.5	101	15	19.3	100	15
2	19.6	15	19.5	100	15	19.7	101	15	19.3	99	15
3	20.6	15	20.9	102	15	21.1	102	15	20.7	101	15
4	21.3	15	21.9	103	15	21.9	103	15	21.8	102	15
5	21.5	15	22.8	106	15	22.5	105	15	22.4	104	15
6	22.2	15	22.8	103	15	23.1	104	15	22.7	102	15
7	23.4	15	23.5	100	15	23.4	100	15	23.5	100	15
8	23.2	15	23.8	103	15	24.0	103	15	24.1	104	15
9	23.7	15	24.3	103	15	24.2	102	15	24.6	104	15
10	23.7	14	23.7	100	15	23.8	100	15	24.7	104	15
11	24.5	14	23.6	96	14	24.5	100	15	24.4	100	14
12	24.4	14	23.9	98	13	24.7	101	15	25.3	104	14
13	24.5	14	24.5	100	12	24.9	102	15	24.9	102	14
14	24.6	14	25.6	104	12	25.3	103	15	25.6	104	14
15	24.8	14	25.2	102	12	25.1	101	15	25.6	103	13
16	25.4	14	25.3	100	12	24.7	97	15	25.7	101	13
17	25.3	14	25.6	101	12	25.3	100	14	25.6	101	13
18	25.8	14	25.7	100	12	24.6	95	14	25.3	98	11
19	26.0	14	25.9	100	12	25.8	99	14	26.3	101	11
20	25.5	14	26.1	102	12	25.2	99	14	26.1	102	11
21	25.7	14	26.4	103	12	26.4	103	12	26.0	101	11
22	26.4	13	26.9	102	12	26.7	101	11	26.4	100	11
23	26.1	13	26.6	102	11	26.6	102	11	27.1	104	11
24	26.7	12	26.7	100	11	26.3	99	11	27.3	102	11
25	27.4	11	27.8	102	10	27.2	99	11	27.8	102	11
26	27.1	11	27.6	102	10	25.7	95	11	28.2	104	11
Mean for weeks											
1-13	22.5		22.7	101		22.9	102		22.9	102	
14-26	25.9		26.3	101		25.8	99		26.4	102	

Hematology

Minimal (less than or equal to 8%) decreases in hematocrit and hemoglobin concentration values occurred in 128 mg/kg females and 256 mg/kg males and females (Tables 5 and E1); a minimal (7%) decrease in erythrocyte count also occurred in 256 mg/kg males. These decreases in erythron were accompanied by minimal (less than or equal to 6%) decreases in mean cell hemoglobin and mean cell hemoglobin concentration values, primarily in the females; the mean cell volume was unaffected. The erythron decrease was also accompanied by an apparent regenerative-type response indicated by an approximate 45% increase in reticulocyte counts in 128 mg/kg females and 256 mg/kg males and females.

TABLE 5
Selected Hematology Data for Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
n	12	10	13	12
Hematocrit (%)	42.9 ± 0.5	41.4 ± 0.7	41.9 ± 0.7	41.0 ± 0.6
Hemoglobin (g/dL)	13.9 ± 0.2	13.2 ± 0.2	13.4 ± 0.2	13.0 ± 0.2**
Erythrocytes (10^6/μL)	9.91 ± 0.15	9.47 ± 0.17	9.65 ± 0.18	9.29 ± 0.18*
Reticulocytes (10^6/μL)	0.15 ± 0.02	0.19 ± 0.02	0.19 ± 0.01	0.22 ± 0.02*
Mean cell volume (fL)	43.3 ± 0.4	43.8 ± 0.2	43.4 ± 0.3	44.2 ± 0.3
Mean cell hemoglobin (pg)	14.0 ± 0.2	14.0 ± 0.1	13.9 ± 0.1	14.0 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.3 ± 0.1	32.0 ± 0.1	32.1 ± 0.2	31.7 ± 0.3*
Female				
n	10	10	11	11
Hematocrit (%)	43.4 ± 0.5	42.6 ± 0.5	41.0 ± 0.8*	41.1 ± 0.5**
Hemoglobin (g/dL)	14.3 ± 0.1	13.8 ± 0.2	13.1 ± 0.3**	13.1 ± 0.1**
Erythrocytes (10^6/μL)	9.84 ± 0.19	9.55 ± 0.13	9.45 ± 0.31	9.67 ± 0.25
Reticulocytes (10^6/μL)	0.15 ± 0.01	0.19 ± 0.01	0.21 ± 0.02*	0.21 ± 0.02*
Mean cell volume (fL)	44.1 ± 0.5	44.6 ± 0.2	43.6 ± 0.6	42.7 ± 0.7
Mean cell hemoglobin (pg)	14.5 ± 0.2	14.5 ± 0.1	14.0 ± 0.2*	13.6 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.1	32.5 ± 0.1**	32.0 ± 0.1**	31.8 ± 0.2**

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

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 skin, thyroid gland, kidney, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions are presented in Tables A1, A2, A3, and A4.

Skin: Dermal administration of sodium bromate for 26 weeks resulted in no squamous cell papillomas at the site of application in males or females and no significant treatment-related changes in the incidences of neoplasms or nonneoplastic lesions of the skin of male mice. Combined incidences of multiple and single squamous cell papillomas of the skin were slightly increased in the 256 mg/kg group of female mice (vehicle control, 5/15; 64 mg/kg, 3/15; 128 mg/kg, 4/15; 256 mg/kg, 9/15; Table A3). The increase was not significant (by the Fisher exact test). Characteristic squamous cell papillomas were pedunculated skin masses consisting of multiple finger-like projections composed of branching fibrous tissue cores covered by hyperplastic epithelium. Other solid skin masses composed of stratified squamous epithelium without projections were still considered papillomas.

Thyroid Gland: Significantly increased treatment-related changes were observed in thyroid glands of both male and female mice (Tables 6, A2, and A4). Changes were more frequent and severe in females. The incidences of follicular cell hypertrophy were significantly increased in all dosed groups of males and females. Follicular hypertrophy was characterized by an increase in the size of cells lining follicles. In animals from the higher dose groups, the follicles became quite small or were completely obliterated by large hypertrophied follicular lining cells. The incidences of follicular secretory depletion were significantly increased in 128 and 256 mg/kg females with a smaller increase in 256 mg/kg males and 64 mg/kg females. The diagnosis of follicular secretory depletion was based primarily on qualitative changes in the colloid rather than the quantity of colloid within follicles. Affected follicles had pale staining colloid that contained basophilic concretion-like structures and were dilated with thinning of the follicular epithelium. These follicles tended to have a more angular appearance than normal round follicles. In animals from the higher dose groups, the pale staining colloid became vacuolated or granular or contained a thickened floccular material. The incidences of lymphocyte cellular infiltrates were significantly increased in 64 and 256 mg/kg females. Lymphocytic infiltration consisted of aggregates of varying numbers of lymphocytes within the stroma among follicles.

TABLE 6
Incidences of Nonneoplastic Lesions of the Thyroid Gland in Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
Number Examined Microscopically	15	15	15	15
Follicular Cell, Hypertrophy[a]	0	7** (1.0)[b]	10** (1.3)	14** (1.4)
Follicle, Depletion Secretory	7 (1.0)	4 (1.0)	5 (1.0)	11 (1.1)
Female				
Number Examined Microscopically	15	15	15	15
Follicular Cell, Hypertrophy	1 (1.0)	9** (1.0)	12** (1.9)	13** (2.8)
Follicle, Depletion Secretory	6 (1.2)	11 (1.2)	13** (1.5)	14** (2.6)
Infiltration Cellular, Lymphocyte	0	6** (1.0)	3 (1.0)	12** (1.3)

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

Kidney: Relative kidney weights were significantly increased in 256 mg/kg males compared to the vehicle controls (Table F1). The incidences of nephropathy were significantly increased in 128 mg/kg males and 256 mg/kg males and females (Tables 7, A2, and A4). These lesions were usually minimal in severity. Nephropathy included unequivocal tubular basophilia (regeneration), tubular dilatation, proteinaceous casts, basement membrane thickening and interstitial inflammation, as well as increased mitotic figures and nuclear pleomorphism.

Spleen: Hematopoietic cell proliferation increased with increasing dose in female mice. Significant increases occurred in 128 and 256 mg/kg females (Tables 7 and A4).

TABLE 7
Incidences of Selected Nonneoplastic Lesions in Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
Kidney[a]	15	15	15	15
Nephropathy[b]	8 (1.0)[c]	8 (1.1)	14* (1.0)	14* (1.1)
Female				
Kidney	15	15	15	15
Nephropathy	8 (1.0)	7 (1.0)	13 (1.0)	15** (1.0)
Spleen	15	15	15	15
Hematopoietic Cell Proliferation	3 (1.7)	5 (1.4)	9* (1.9)	10* (2.1)

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

39-Week Dermal Study in Tg.AC Hemizygous Mice

Survival

Estimates of 39-week survival probabilities for male and female mice are shown in Table 8. Survival of all dosed groups was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of 128 mg/kg male mice were less than those of the vehicle controls at the end of the study (Figure 2, Tables 9 and 10), and those of 256 mg/kg males were generally less after week 28. Mean body weights of 64 and 128 mg/kg females were generally less than those of the vehicle controls after week 12, and those of 256 mg/kg females were less after week 18. No clinical findings were attributed to sodium bromate administration.

Table 8
Survival of Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
Animals initially in study	10	10	10	10
Moribund	1	0	0	2
Natural deaths	1	2	2	0
Animals surviving to study termination	8	8	8	8
Percent probability of survival at end of study[a]	80	80	80	80
Mean survival (days)[b]	253	257	265	247
Survival analysis[c]	P=1.000N	P=1.000N	P=1.000N	P=1.000N
Female				
Animals initially in study	10	10	10	10
Missing[d]	1	0	0	0
Moribund	1	1	2	1
Natural deaths	1	2	0	1
Animals surviving to study termination	7	7	8	8
Percent probability of survival at end of study	78	70	80	80
Mean survival (days)	264	226	252	265
Survival analysis	P=0.891N	P=0.929	P=1.000N	P=1.000N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dose group is indicated by **N**.
[d] Censored from survival analysis

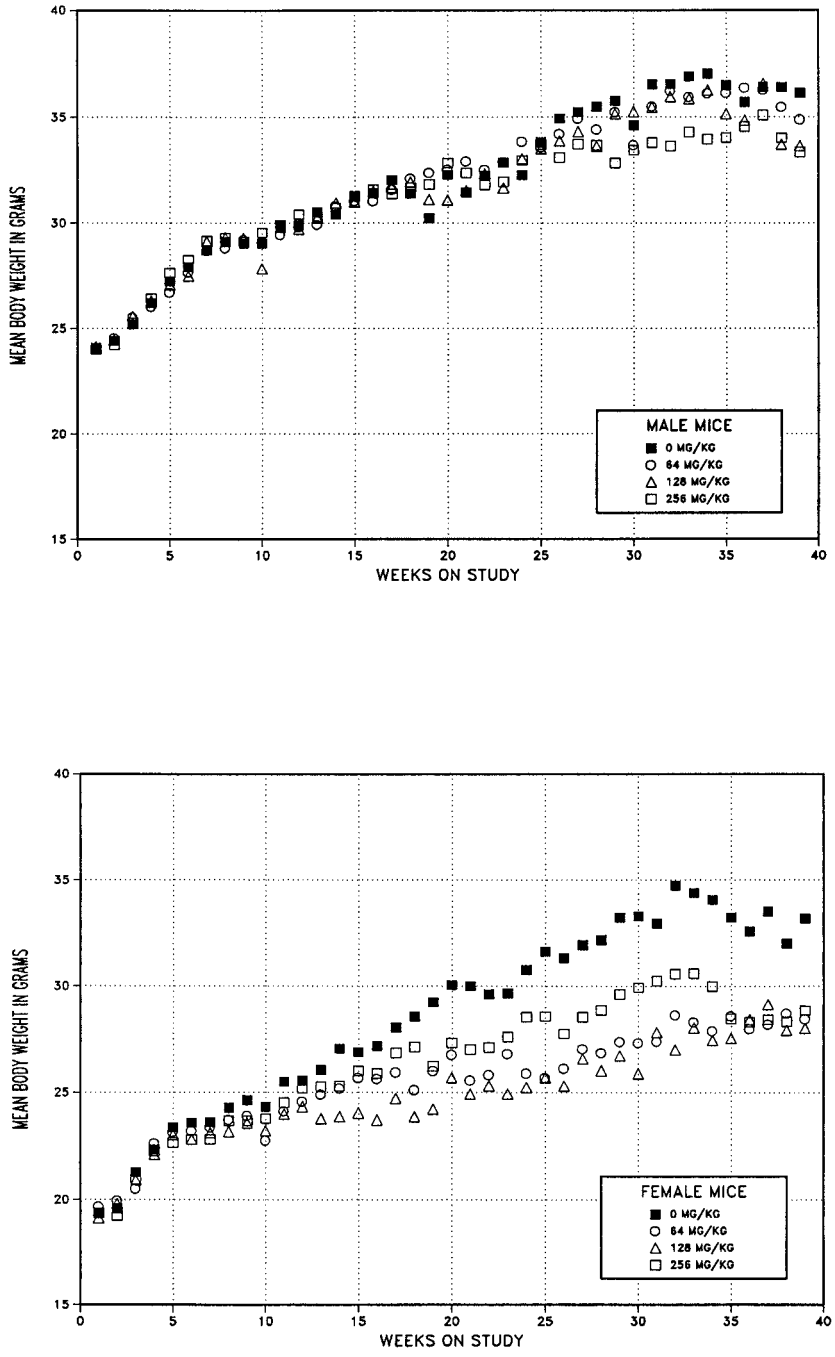


FIGURE 2
Growth Curves for Male and Female Tg.AC Hemizygous Mice Administered Sodium Bromate Dermally for 39 Weeks

TABLE 9
Mean Body Weights and Survival of Male Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

Weeks on Study	Vehicle Control		64 mg/kg			128 mg/kg			256 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.1	10	24.1	100	10	24.1	100	10	24.0	100	10
2	24.4	10	24.5	100	10	24.5	100	10	24.2	99	10
3	25.2	10	25.5	101	10	25.6	102	10	25.3	100	10
4	26.2	10	26.0	99	10	26.3	100	10	26.4	101	10
5	27.2	10	26.7	98	10	27.1	100	10	27.6	102	10
6	27.9	10	27.7	99	10	27.5	99	10	28.3	101	10
7	28.7	10	28.7	100	10	29.1	101	10	29.2	102	10
8	29.1	10	28.8	99	10	29.3	101	10	29.3	101	10
9	29.0	10	29.2	101	10	29.3	101	10	29.1	100	10
10	29.0	10	29.1	100	10	27.8	96	10	29.5	102	10
11	29.9	10	29.4	98	10	29.8	100	10	29.9	100	9
12	29.9	10	29.8	100	10	29.7	99	10	30.4	102	9
13	30.5	10	29.9	98	10	30.2	99	10	30.3	99	9
14	30.4	10	30.8	101	10	31.0	102	10	30.7	101	9
15	31.3	10	31.0	99	10	31.0	99	10	31.3	100	9
16	31.4	10	31.0	99	10	31.5	100	10	31.6	101	9
17	32.0	10	31.6	99	10	31.7	99	10	31.4	98	9
18	31.4	10	32.1	102	10	31.9	102	10	31.7	101	9
19	30.2	10	32.4	107	10	31.1	103	10	31.8	105	9
20	32.3	10	32.5	101	10	31.1	96	10	32.8	102	9
21	31.5	9	32.9	104	9	31.5	100	10	32.4	103	9
22	32.2	9	32.5	101	9	32.3	100	10	31.8	99	9
23	32.9	9	32.9	100	9	31.7	96	10	32.0	97	9
24	32.3	9	33.8	105	9	33.0	102	10	33.0	102	9
25	33.8	9	33.6	99	9	33.5	99	10	33.7	100	9
26	34.9	9	34.2	98	9	33.9	97	10	33.1	95	9
27	35.2	9	34.9	99	9	34.3	97	10	33.7	96	9
28	35.5	9	34.4	97	9	33.6	95	10	33.7	95	9
29	35.8	9	35.2	98	9	35.2	98	10	32.8	92	9
30	34.6	9	33.7	97	9	35.3	102	10	33.5	97	9
31	36.5	9	35.5	97	9	35.5	97	10	33.8	93	9
32	36.5	8	36.2	99	9	36.0	99	10	33.6	92	9
33	36.9	8	35.9	97	9	35.9	97	9	34.3	93	8
34	37.0	8	36.1	98	9	36.3	98	9	34.0	92	8
35	36.5	8	36.1	99	9	35.1	96	9	34.0	93	8
36	35.7	8	36.4	102	9	34.9	98	9	34.6	97	8
37	36.4	8	36.3	100	8	36.6	101	8	35.1	96	8
38	36.4	8	35.5	98	8	33.7	93	8	34.0	93	8
39	36.1	8	34.9	97	8	33.7	93	8	33.4	93	8
Mean for weeks											
1-13	27.8		27.6	100		27.7	100		28.0	101	
14-39	34.1		33.9	100		33.5	99		33.0	97	

TABLE 10
Mean Body Weights and Survival of Female Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

Weeks on Study	Vehicle Control		64 mg/kg			128 mg/kg			256 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.4	10	19.7	102	10	19.1	99	10	19.4	100	10
2	19.6	10	20.0	102	10	19.8	101	10	19.2	98	10
3	21.3	10	20.5	96	10	20.9	98	10	21.0	99	10
4	22.4	10	22.6	101	10	22.1	99	10	22.3	100	10
5	23.4	9	23.2	99	10	23.0	98	10	22.7	97	10
6	23.6	9	23.2	98	10	22.8	97	10	22.8	97	10
7	23.6	9	23.4	99	10	23.1	98	10	22.8	97	10
8	24.3	9	23.7	98	10	23.2	96	10	23.7	98	10
9	24.6	9	23.9	97	10	23.6	96	10	23.7	96	10
10	24.3	9	22.8	94	9	23.2	96	10	23.8	98	10
11	25.5	9	24.1	95	9	24.0	94	10	24.5	96	10
12	25.6	9	24.6	96	9	24.3	95	10	25.2	98	10
13	26.1	9	24.9	95	9	23.8	91	10	25.3	97	10
14	27.1	9	25.2	93	9	23.9	88	10	25.3	93	10
15	26.9	9	25.7	96	9	24.1	90	10	26.0	97	10
16	27.2	9	25.6	94	9	23.7	87	10	25.9	95	10
17	28.0	9	25.9	93	9	24.7	88	10	26.9	96	10
18	28.6	9	25.1	88	9	23.9	84	10	27.1	95	10
19	29.2	9	26.0	89	9	24.2	83	10	26.3	90	10
20	30.1	9	26.8	89	9	25.7	85	9	27.3	91	10
21	30.0	9	25.6	85	9	24.9	83	9	27.0	90	10
22	29.6	9	25.8	87	7	25.3	86	9	27.1	92	10
23	29.7	9	26.8	90	7	24.9	84	9	27.6	93	10
24	30.8	9	25.9	84	7	25.2	82	9	28.5	93	10
25	31.6	9	25.7	81	7	25.7	81	9	28.6	91	10
26	31.3	9	26.1	83	7	25.3	81	9	27.8	89	10
27	31.9	9	27.0	85	7	26.6	83	9	28.5	89	10
28	32.2	9	26.8	83	7	26.0	81	9	28.9	90	10
29	33.2	9	27.4	83	7	26.7	80	9	29.6	89	10
30	33.3	9	27.3	82	7	25.9	78	9	29.9	90	10
31	33.0	9	27.4	83	7	27.8	84	9	30.3	92	10
32	34.7	8	28.6	82	7	27.0	78	9	30.6	88	9
33	34.4	8	28.3	82	7	28.0	81	8	30.6	89	9
34	34.1	8	27.9	82	7	27.5	81	8	30.0	88	9
35	33.2	8	28.6	86	7	27.6	83	8	28.5	86	9
36	32.6	8	28.0	86	7	28.4	87	8	28.3	87	9
37	33.5	7	28.2	84	7	29.2	87	8	28.4	85	9
38	32.0	7	28.7	90	7	27.9	87	8	28.3	88	8
39	33.2	7	28.5	86	7	28.0	84	8	28.9	87	8
Mean for weeks											
1-13	23.4		22.8	98		22.5	97		22.8	98	
14-39	31.2		26.9	86		26.1	84		28.2	90	

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 skin, forestomach, thyroid gland, kidney, and testes. Summaries of the incidences of neoplasms and nonneoplastic lesions are presented in Tables A5, A6, A7, and A8.

Skin: Dermal administration of sodium bromate for 39 weeks resulted in no significant treatment-related increases in neoplasms or nonneoplastic lesions of the skin of either male or female Tg.AC hemizygous mice (Tables A5, A6, A7, and A8).

Forestomach: Combined incidences of multiple and single squamous cell papillomas were increased in the 128 and 256 mg/kg groups of female mice (vehicle control, 2/9; 64 mg/kg, 2/10; 128 mg/kg, 7/10; 256 mg/kg, 4/10; Table A7); the increases were not significant. Forestomach neoplasms did not occur in male mice (Table A5). Squamous cell papillomas of the forestomach were similar in microscopic appearance to those described in the skin at 26 weeks.

Thyroid Gland: Significantly increased treatment-related changes were observed in thyroid glands of male and female mice (Tables 11, A6, and A8). As with the 26-week study, changes were more frequent and severe in females. The microscopic changes were similar to those observed at 26 weeks. The incidences of follicular cell hypertrophy were significantly increased in all dosed groups of males and females; and the severities were increased in females (Tables 11, A6, and A8). Incidences of lymphocyte cellular infiltrates increased with increasing dose in females; and the incidences were significantly increased in the 128 and 256 mg/kg groups (Tables 11 and A8). The incidence of follicular secretory depletion was significantly increased in 128 and 256 mg/kg females, and the severity of this lesion increased with increasing dose.

Kidney: Absolute kidney weights were significantly decreased in 256 mg/kg females (Table F2). Relative kidney weights were significantly increased in all dosed groups of males compared to the vehicle control group.

The incidence of nephropathy was significantly increased in 256 mg/kg females (Tables 11 and A8). The lesions were minimal to mild in severity. The incidence of renal cell hypertrophy was slightly increased in 256 mg/kg females (Tables 11 and A8). Renal tubule hypertrophy referred to tubules having palely stained enlarged epithelial cells that did not have features suggesting degeneration.

Testes: Absolute testis weights were significantly decreased in 256 mg/kg males. The incidences of germinal epithelium degeneration increased with increasing dose, and the increase was significant in 256 mg/kg males (Tables 11 and A6). Microscopically, the degeneration consisted of vacuolar changes with partial to complete loss of the germinal epithelium within seminiferous tubules leaving only Sertoli cells and resulting in shrinkage and atrophy of the affected tubules.

TABLE 11
Incidences of Selected Nonneoplastic Lesions in Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
Thyroid Gland[a]	10	10	10	10
Follicular Cell, Hypertrophy[b]	0	9** (1.0)[c]	8** (1.5)	8** (1.9)
Testes	10	10	10	10
Germinal Epithelium, Degeneration	1 (3.0)	2 (1.5)	3 (3.0)	6* (2.8)
Female				
Thyroid Gland	9	10	10	10
Follicular Cell, Hypertrophy	1 (1.0)	9** (1.6)	9** (2.9)	10** (3.3)
Infiltration Cellular, Lymphocyte	0	2 (1.5)	5* (1.2)	10** (1.4)
Follicle, Depletion Secretory	5 (1.2)	8 (1.5)	10* (2.7)	10* (3.5)
Kidney	9	10	10	10
Nephropathy	5 (1.0)	6 (1.0)	8 (1.0)	10* (1.3)
Renal Tubule, Hypertrophy	0	0	0	4 (1.0)

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

27-Week Drinking Water Study in Tg.AC Hemizygous Mice

Positive Control Tg.AC Hemizygous Mice

12-*O*-tetradecanoylphorbol-13-acetate (TPA) (1.25 µg) was administered dermally to groups of 15 males and 15 females three times weekly for 26 weeks. Papillomas were first observed at week 11 for males and week 9 for females; 80% of males and females developed more than 20 papillomas each before scheduled study termination (data not shown). This is consistent with historical rates found in other studies (Tennant *et al.*, 2001).

Survival

Estimates of 27-week survival probabilities for male and female mice are shown in Table 12. Survival of all exposed groups was similar to that of the control groups.

Body Weights and Clinical Findings

Mean body weights of 800 mg/L males were less than those of the controls after week 5. Mean body weights of 400 mg/L males and 800 mg/L females were less than those of the control groups after week 9 (Figure 3; Tables 13 and 14). Water consumption by exposed mice was generally similar to that by controls throughout the study (Tables H1 and H2). Drinking water concentrations of 80, 400, and 800 mg/L resulted in average daily doses of approximately 13, 63, and 129 mg sodium bromate/kg body weight to male mice and 15, 72, and 148 mg/kg to female mice. No clinical findings were attributed to the administration of sodium bromate.

Table 12
Survival of Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Animals initially in study	15	15	15	15
Moribund	0	0	1	0
Natural deaths	2	2	0	1
Animals surviving to study termination	13	13	14	14
Percent probability of survival at end of study[a]	87	87	93	93
Mean survival (days)[b]	172	181	180	181
Survival analysis[c]	P=0.620N	P=1.000N	P=0.984N	P=0.984N
Female				
Animals initially in study	15	15	15	15
Moribund	2	1	0	0
Natural deaths	3	5	5	3
Animals surviving to study termination	10	9	10	12
Percent probability of survival at end of study	67	60	67	80
Mean survival (days)	159	149	164	159
Survival analysis	P=0.414N	P=0.905	P=1.000N	P=0.728N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] 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 exposure group is indicated by **N**.

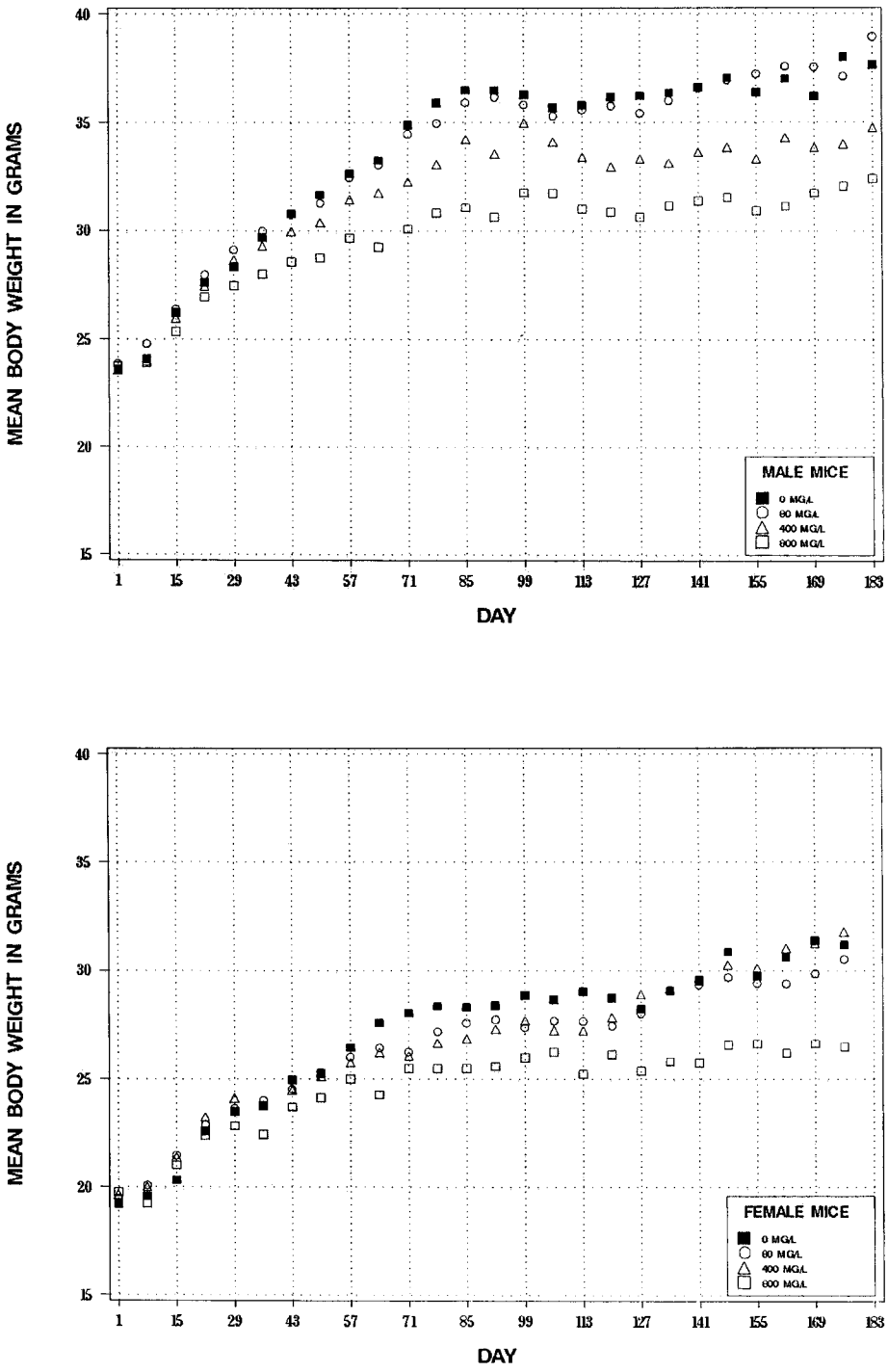


FIGURE 3
Growth Curves for Male and Female Tg.AC Hemizygous Mice Exposed to Sodium Bromate in Drinking Water for 27 Weeks

TABLE 13
Mean Body Weights and Survival of Male Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.6	15	23.9	101	15	23.6	100	15	23.8	101	15
2	24.1	15	24.8	103	15	24.0	100	15	23.9	99	15
3	26.2	15	26.4	101	15	26.0	99	15	25.3	97	15
4	27.6	15	27.9	101	15	27.4	99	15	26.9	98	15
5	28.3	15	29.1	103	15	28.6	101	15	27.4	97	15
6	29.7	14	30.0	101	15	29.3	99	15	28.0	94	15
7	30.8	14	30.7	100	15	29.9	97	15	28.6	93	15
8	31.7	14	31.3	99	15	30.4	96	15	28.7	91	15
9	32.6	14	32.4	99	15	31.4	96	15	29.6	91	15
10	33.3	14	33.0	99	15	31.7	95	15	29.2	88	15
11	34.9	14	34.5	99	15	32.3	93	15	30.1	86	15
12	35.9	14	35.0	98	15	33.1	92	15	30.8	86	15
13	36.5	14	35.9	98	15	34.2	94	15	31.1	85	15
14	36.5	14	36.2	99	15	33.6	92	15	30.6	84	15
15	36.3	14	35.8	99	15	35.0	96	15	31.7	87	15
16	35.7	14	35.3	99	15	34.1	96	15	31.7	89	15
17	35.8	14	35.6	99	15	33.4	93	15	31.0	87	15
18	36.2	14	35.8	99	15	33.0	91	15	30.8	85	15
19	36.2	14	35.4	98	15	33.3	92	15	30.6	85	15
20	36.4	14	36.0	99	15	33.1	91	15	31.2	86	15
21	36.6	14	36.6	100	15	33.6	92	15	31.4	86	15
22	37.1	14	37.0	100	15	33.9	91	14	31.5	85	15
23	36.4	14	37.2	102	14	33.3	92	14	30.9	85	15
24	37.0	14	37.6	102	14	34.3	93	14	31.1	84	14
25	36.2	14	37.6	104	14	33.9	94	14	31.7	88	14
26	38.0	13	37.1	98	14	34.0	90	14	32.1	85	14
Mean for weeks											
1-13	30.4		30.4	100		29.4	97		28.0	93	
14-26	36.5		36.4	100		33.7	93		31.3	86	

TABLE 14
Mean Body Weights and Survival of Female Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.2	15	19.4	101	15	19.7	103	15	19.8	103	15
2	19.6	15	20.1	103	15	20.0	102	15	19.2	98	15
3	20.3	15	21.5	106	15	21.4	105	15	21.0	103	14
4	22.6	15	22.9	101	15	23.2	103	15	22.4	99	14
5	23.5	14	23.6	100	15	24.1	103	14	22.8	97	13
6	23.8	14	24.0	101	15	23.8	100	14	22.4	94	13
7	25.0	14	24.5	98	15	24.5	98	14	23.7	95	13
8	25.3	13	25.3	100	14	25.1	99	14	24.1	95	13
9	26.4	13	26.0	99	13	25.8	98	14	25.0	95	13
10	27.6	13	26.4	96	13	26.2	95	14	24.3	88	13
11	28.0	13	26.2	94	13	26.0	93	14	25.5	91	13
12	28.4	13	27.2	96	13	26.7	94	14	25.5	90	13
13	28.3	13	27.6	98	13	26.9	95	14	25.5	90	13
14	28.4	13	27.7	98	12	27.3	96	13	25.6	90	13
15	28.9	13	27.4	95	12	27.7	96	13	26.0	90	13
16	28.7	13	27.7	97	11	27.2	95	13	26.2	91	13
17	29.0	13	27.7	96	11	27.2	94	13	25.2	87	13
18	28.7	13	27.4	96	11	27.8	97	13	26.1	91	13
19	28.2	12	28.0	99	11	28.9	103	13	25.4	90	13
20	29.1	12	29.0	100	11	29.2	100	13	25.8	89	13
21	29.6	12	29.3	99	10	29.5	100	13	25.8	87	13
22	30.9	12	29.7	96	9	30.3	98	13	26.6	86	12
23	29.8	12	29.4	99	9	30.1	101	12	26.6	89	12
24	30.6	12	29.4	96	9	31.0	101	11	26.2	86	12
25	31.4	12	29.8	95	9	31.2	99	11	26.6	85	12
26	31.2	11	30.5	98	9	31.8	102	11	26.5	85	12
Mean for weeks											
1-13	24.5		24.2	99		24.1	99		23.2	95	
14-26	29.6		28.7	97		29.2	99		26.0	88	

Hematology

In the drinking water study, the erythron demonstrated effects that were similar to those observed in the dermal study. There were minimal (less than or equal to 10%) decreases in hematocrit, hemoglobin concentration, and erythrocyte count values that occurred primarily in 400 and 800 mg/L females (Tables 15 and E2). There were also decreases of 5% or less in the mean cell hemoglobin and mean cell hemoglobin concentration values, but these occurred primarily in exposed males. Reticulocyte counts were increased in 400 mg/L males (35%) and 800 mg/L males (67%) and females (130%).

TABLE 15
Selected Hematology Data for Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	12	13	13	14
Hematocrit (%)	40.8 ± 0.5	41.0 ± 0.4	40.1 ± 0.4	41.7 ± 0.4
Hemoglobin (g/dL)	13.3 ± 0.2	13.2 ± 0.1	12.8 ± 0.2*	13.0 ± 0.2
Erythrocytes (10^6/µL)	9.31 ± 0.15	9.40 ± 0.13	9.13 ± 0.12	9.56 ± 0.08
Reticulocytes (10^6/µL)	0.14 ± 0.01	0.15 ± 0.01	0.19 ± 0.01**	0.24 ± 0.02**
Mean cell volume (fL)	43.9 ± 0.2	43.6 ± 0.3	44.0 ± 0.3	43.7 ± 0.3
Mean cell hemoglobin (pg)	14.3 ± 0.1	14.1 ± 0.1	14.0 ± 0.1*	13.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.3 ± 0.0*	31.9 ± 0.1**	31.1 ± 0.2**
Female				
n	10	9	9	12
Hematocrit (%)	44.4 ± 0.7	44.5 ± 0.7	42.4 ± 0.8	41.4 ± 0.6**
Hemoglobin (g/dL)	14.4 ± 0.2	14.5 ± 0.3	13.6 ± 0.3	13.0 ± 0.2**
Erythrocytes (10^6/µL)	10.11 ± 0.18	9.96 ± 0.20	9.50 ± 0.29*	9.12 ± 0.21**
Reticulocytes (10^6/µL)	0.14 ± 0.01	0.15 ± 0.02	0.17 ± 0.02	0.33 ± 0.04**
Mean cell volume (fL)	44.0 ± 0.5	44.7 ± 0.5	44.8 ± 0.6	45.5 ± 0.5
Mean cell hemoglobin (pg)	14.3 ± 0.2	14.6 ± 0.2	14.4 ± 0.2	14.2 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.4 ± 0.2	32.6 ± 0.1	32.0 ± 0.1	31.3 ± 0.1**

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

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 thyroid gland, kidney, pituitary gland, and mandibular lymph node. Summaries of the incidences of neoplasms and nonneoplastic lesions are presented in Tables B1, B2, B3, and B4.

Thyroid Gland: Significantly increased treatment-related changes were observed in the thyroid glands of male and female mice (Tables 16, B2, and B4). Male and female groups had similar incidence rates with increased severities in females. The incidences of follicular cell hypertrophy and follicular secretory depletion were significantly increased in the 400 and 800 mg/L groups of males and females (Tables 16, B2, and B4). The incidences of lymphocyte cellular infiltrates were significantly increased in the 400 and 800 mg/L females.

Kidney: Absolute kidney weights were significantly decreased in 800 mg/L females when compared to controls (Table F3). Relative kidney weights were significantly increased in 400 and 800 mg/L males. The incidences of nephropathy were significantly increased in all exposed groups of males and in the 400 and 800 mg/L female groups (Tables 16, B2, and B4). These lesions were minimal to mild in severity. The incidences of renal tubule degeneration were significantly increased in 800 mg/L males and females (Tables 16, B2, and B4). Renal tubule degeneration consisted of tubule cell changes including vacuolization or flocculent cytoplasm in epithelial cells, necrosis of tubule epithelial cells, and faint basophilic cellular staining. The incidences of renal cell hypertrophy were significantly increased in 400 and 800 mg/L females. Renal tubule hypertrophy referred to tubules having palely stained enlarged epithelial cells that did not show other features suggesting degeneration.

Pituitary Gland: The incidence of pars distalis hypertrophy was significantly increased in 800 mg/L females (Tables 16 and B4). The hypertrophy was characterized by an increase in the size of chromophobes.

Lymph Node, Mandibular: The incidences of lymphoid hyperplasia were significantly increased in the 80 and 800 mg/L female groups (0 mg/L, 0/15; 80 mg/L, 4/15; 400 mg/L, 2/15; 800 mg/L, 5/15; Table B4). These lesions were characterized by increased numbers of lymphocytes and an increase in the size of the lymph nodes.

TABLE 16
Incidences of Selected Nonneoplastic Lesions in Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Thyroid Gland[a]	15	14	15	15
Follicular Cell, Hypertrophy[b]	1 (2.0)[c]	2 (1.5)	12** (1.6)	15** (2.0)
Follicular Depletion, Secretory	4 (1.0)	6 (1.0)	15** (1.1)	15** (1.3)
Kidney	15	15	15	15
Nephropathy	1 (1.0)	7* (1.0)	10** (1.0)	14** (1.6)
Renal Tubule, Degeneration	0	0	0	10** (1.3)
Female				
Thyroid Gland	15	13	13	15
Follicular Cell, Hypertrophy	2 (1.0)	2 (1.0)	11** (1.9)	13** (3.2)
Follicular Depletion, Secretory	7 (1.1)	7 (1.6)	11* (1.8)	14** (3.1)
Infiltration Cellular, Lymphocyte	0	0	5* (1.0)	11** (1.5)
Kidney	15	15	15	15
Nephropathy	2 (1.0)	2 (1.0)	10** (1.0)	13** (1.8)
Renal Tubule, Degeneration	0	0	2 (1.0)	8** (1.9)
Renal Tubule, Hypertrophy	0	1 (1.0)	5* (1.0)	12** (1.8)
Pituitary Gland	15	15	15	15
Pars Distalis, Hypertrophy	0	0	0	6** (2.2)

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

43-Week Drinking Water Study in Tg.AC Hemizygous Mice

Survival

Estimates of 43-week survival probabilities for male and female mice are shown in Table 17. Although not statistically significant, survival was decreased in 400 mg/L females and 800 mg/L males and females compared to that of the control groups.

Body Weights and Clinical Findings

Mean body weights of 400 and 800 mg/L male mice were less than those of the controls beginning at approximately weeks 35 and 3 of the study, respectively. Body weights of 80 and 800 mg/L females were less than those of the controls beginning at weeks 24 and 13 of the study, respectively (Tables 18 and 19; Figure 4). Water consumption by exposed mice was generally similar to that by controls throughout the study (Tables H3 and H4). Drinking water concentrations of 80, 400, and 800 mg/L resulted in average daily doses of approximately 11, 52, and 131 mg/kg to male mice and 15, 65, and 152 mg/kg to female mice. No clinical findings were attributed to sodium bromate administration.

Table 17
Survival of Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Animals initially in study	10	10	10	10
Moribund	2	2	4	3
Natural deaths	2	1	0	3
Animals surviving to study termination	6	7	6	4
Percent probability of survival at end of study[a]	60	70	60	40
Mean survival (days)[b]	251	244	263	260
Survival analysis[c]	P=0.515	P=1.000N	P=1.000N	P=0.826
Female				
Animals initially in study	10	10	10	10
Moribund	3	4	4	7
Natural deaths	0	1	2	1
Animals surviving to study termination	7	5	4	2
Percent probability of survival at end of study	70	50	40	20
Mean survival (days)	246	249	238	194
Survival analysis	P=0.030	P=0.740	P=0.470	P=0.089

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A lower mortality in an exposure group is indicated by **N**.

TABLE 18
Mean Body Weights and Survival of Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.3	10	23.6	101	10	23.6	101	10	23.6	101	10
2	24.4	10	24.3	100	10	24.8	102	10	23.2	95	10
3	25.9	10	25.0	97	10	26.1	101	10	24.1	93	10
4	28.2	10	28.0	99	10	28.4	101	10	25.8	92	10
5	29.0	10	29.3	101	10	29.3	101	10	27.4	95	10
6	29.4	10	30.2	103	10	30.6	104	10	28.7	98	10
7	30.9	10	31.7	103	10	30.8	100	10	29.4	95	10
8	32.1	10	32.4	101	10	31.8	99	10	29.7	93	10
9	32.5	10	33.1	102	10	32.1	99	10	30.6	94	10
10	33.4	10	34.2	102	10	32.6	98	10	30.5	91	10
11	33.3	10	33.9	102	10	32.8	99	10	30.1	90	10
12	34.3	10	35.0	102	10	33.2	97	10	30.3	88	10
13	35.1	10	36.0	103	10	33.9	97	10	30.7	88	10
14	35.6	10	36.5	103	9	34.2	96	10	30.4	85	10
15	36.2	9	37.5	104	8	34.9	96	10	30.4	84	10
16	34.8	9	36.7	106	8	33.9	97	10	30.2	87	10
17	36.2	9	37.1	103	8	34.3	95	10	31.4	87	10
18	36.8	9	37.7	102	8	34.8	95	10	31.6	86	10
19	36.7	9	36.3	99	8	34.5	94	10	32.1	88	9
20	36.8	9	37.6	102	8	35.8	97	10	32.6	89	9
21	37.1	9	37.2	100	8	36.0	97	10	32.2	87	9
22	38.1	9	37.2	98	8	36.0	95	9	32.1	84	9
23	37.8	9	36.7	97	8	36.5	97	9	31.4	83	9
24	37.8	9	36.6	97	8	35.6	94	9	31.4	83	9
25	37.7	9	36.5	97	8	35.8	95	9	31.6	84	9
26	38.7	9	37.5	97	8	36.2	94	9	32.2	83	9
27	38.3	9	37.4	98	8	35.8	94	9	32.3	84	9
28	39.6	8	37.2	94	8	38.8	98	8	33.0	83	9
29	39.2	8	40.2	103	7	37.5	96	8	32.7	83	9
30	38.4	8	39.5	103	7	37.2	97	8	32.9	86	9
31	38.0	8	40.2	106	7	37.6	99	8	32.5	86	9
32	37.9	8	39.9	105	7	37.8	100	8	33.1	87	8
33	39.3	7	40.9	104	7	38.1	97	8	33.6	86	8
34	39.1	7	40.8	104	7	37.0	95	8	33.6	86	8
35	42.7	6	41.2	97	7	37.7	88	8	32.3	76	8
36	42.6	6	41.9	98	7	37.7	89	8	32.5	76	8
37	42.5	6	41.7	98	7	39.6	93	7	32.3	76	7
38	42.6	6	41.0	96	7	39.3	92	7	30.6	72	7
39	43.2	6	42.7	99	7	38.6	89	7	30.1	70	6
40	43.8	6	42.0	96	7	39.1	89	7	29.0	66	6
41	43.0	6	42.2	98	7	40.7	95	6	29.0	67	5
42	42.1	6	42.1	100	7	40.6	96	6	29.9	71	4
Mean for weeks											
1-13	30.1		30.5	101		30.0	100		28.0	93	
14-42	39.1		39.0	100		37.0	95		31.7	82	

TABLE 19
Mean Body Weights and Survival of Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.2	10	19.5	102	10	19.2	100	10	19.2	100	10
2	19.6	10	19.3	99	10	19.7	101	10	19.3	99	10
3	20.3	10	20.6	102	10	20.4	101	10	21.7	107	9
4	23.0	10	22.0	96	10	22.9	100	10	22.7	99	9
5	23.9	10	23.7	99	10	23.8	100	10	23.4	98	9
6	25.1	10	24.6	98	10	24.6	98	10	24.1	96	9
7	24.6	10	25.1	102	9	24.8	101	10	24.4	99	9
8	26.2	10	25.8	99	9	25.7	98	10	24.9	95	9
9	25.0	10	26.2	105	9	25.7	103	10	25.2	101	9
10	25.6	9	26.3	103	9	26.0	102	10	25.1	98	9
11	25.3	9	26.3	104	9	25.2	100	10	24.6	97	9
12	25.8	9	26.6	103	9	26.2	102	10	24.6	95	9
13	25.8	9	27.1	105	9	27.1	105	10	24.1	93	9
14	26.1	9	27.4	105	9	27.0	103	10	24.0	92	9
15	27.6	8	28.5	103	9	27.4	99	10	25.2	91	8
16	28.5	8	27.4	96	9	26.8	94	10	24.6	86	8
17	28.8	8	28.1	98	9	28.2	98	10	24.9	87	8
18	28.9	8	29.2	101	9	29.0	100	9	27.0	93	7
19	30.4	8	29.6	97	9	30.0	99	9	26.4	87	7
20	29.5	8	29.7	101	9	30.1	102	9	26.4	90	7
21	30.2	8	30.1	100	9	29.8	99	9	26.4	87	7
22	30.5	8	29.7	97	8	28.3	93	8	26.5	87	7
23	29.8	8	29.9	100	8	28.6	96	8	25.9	87	7
24	32.1	8	29.5	92	8	29.9	93	8	25.2	79	7
25	31.8	8	29.7	93	8	30.3	95	8	25.9	81	7
26	32.1	8	29.5	92	8	31.7	99	7	26.0	81	7
27	33.8	8	29.2	86	8	32.1	95	7	26.6	79	7
28	34.0	8	30.3	89	8	32.8	97	7	27.1	80	6
29	34.2	8	29.9	87	8	33.3	97	7	26.4	77	6
30	33.4	8	30.0	90	8	34.2	102	6	27.2	81	4
31	33.4	8	29.7	89	8	34.4	103	6	27.8	83	4
32	33.6	8	29.8	89	8	33.6	100	6	28.3	84	4
33	34.6	8	29.5	85	8	34.8	101	6	28.3	82	4
34	35.3	8	28.9	82	8	35.2	100	6	27.4	78	4
35	34.9	8	28.3	81	8	34.8	100	6	28.8	83	4
36	34.8	7	29.7	85	8	35.6	102	6	28.3	81	4
37	35.3	7	29.1	82	8	36.2	103	6	28.5	81	4
38	35.1	7	29.4	84	7	35.6	101	6	28.7	82	4
39	34.8	7	29.5	85	7	35.1	101	6	26.9	77	4
40	34.7	7	29.8	86	7	35.1	101	6	24.0	69	3
41	33.9	7	29.2	86	7	33.9	100	6	23.6	70	2
42	33.6	7	29.4	88	5	37.8	113	4	23.1	69	2
Mean for weeks											
1-13	23.8		24.1	101		23.9	101		23.3	98	
14-42	32.3		29.3	91		32.1	100		26.4	82	

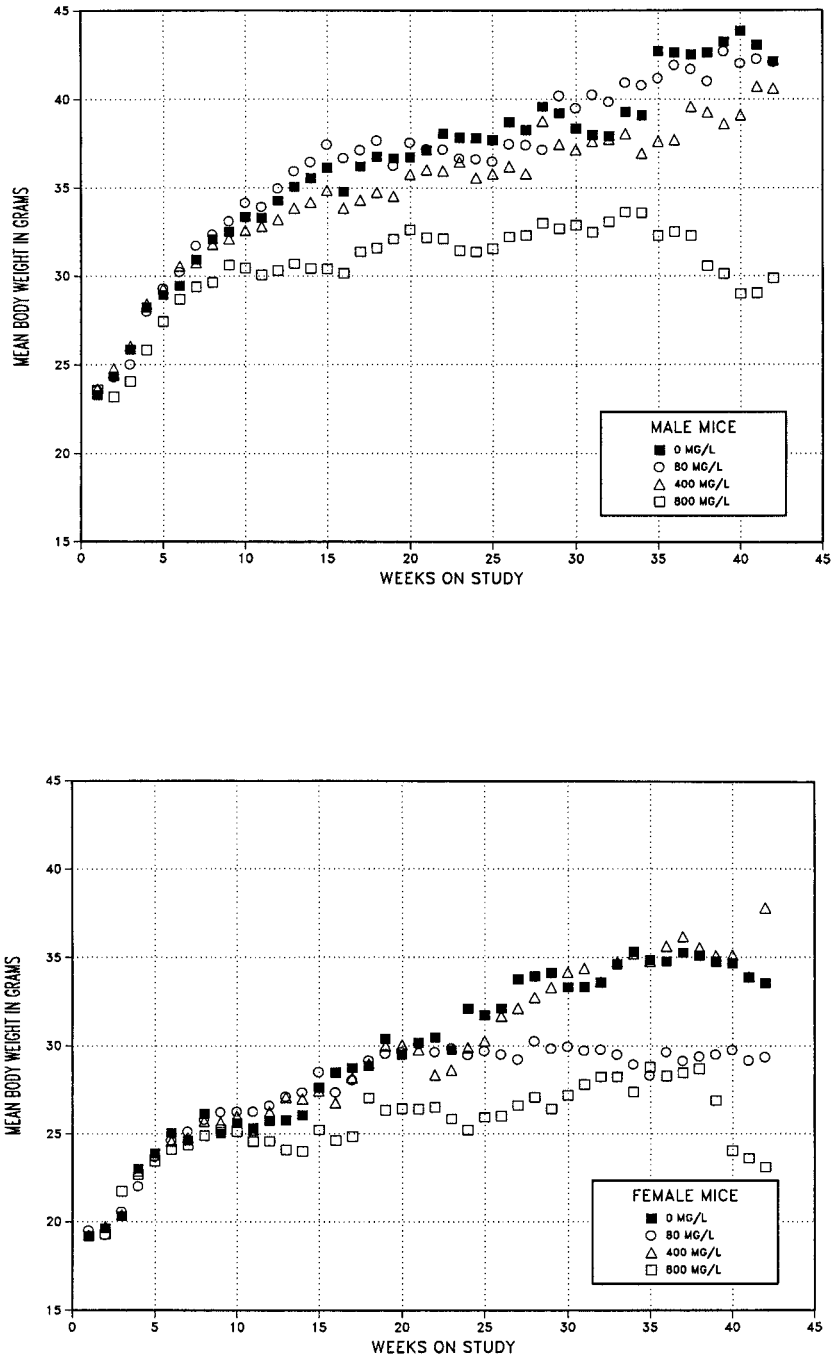


FIGURE 4
Growth Curves for Male and Female Tg.AC Hemizygous Mice Exposed to Sodium Bromate in Drinking Water for 43 Weeks

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 thyroid gland, kidney, epididymis, testes, pituitary gland, thymus, and forestomach. Summaries of the incidences of neoplasms and nonneoplastic lesions are presented in Tables B5, B6, B7, and B8.

Thyroid Gland: Significant treatment-related changes were observed in thyroid glands of male and female mice (Tables 20, B6, and B8). The microscopic changes were similar to those observed at 27 weeks. The incidences of follicular cell hypertrophy were significantly increased in all exposed groups of males and females (Tables 20, B6, and B8). The severities increased with increasing exposure concentration in males and females. The incidences of follicular secretory depletion were increased significantly in all exposed groups of females, and severities increased with increasing exposure concentration. Incidences of lymphocyte cellular infiltrates increased with increasing exposure concentration in females (Tables 20 and B8). Significant increases in incidences occurred in 800 mg/L males and in 400 and 800 mg/L females.

TABLE 20
Incidences of Nonneoplastic Lesions of the Thyroid Gland in Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Number Examined Microscopically	10	10	10	9
Follicular Cell, Hypertrophy[a]	0	6** (1.0)[b]	8** (2.0)	8** (3.5)
Infiltration Cellular, Lymphocyte	0	0	0	4* (1.8)
Female				
Number Examined Microscopically	10	9	10	10
Follicular Cell, Hypertrophy	0	8** (1.0)	10** (2.6)	10** (3.3)
Follicle, Depletion Secretory	1 (2.0)	8** (1.3)	9** (3.0)	10** (3.3)
Infiltration Cellular, Lymphocyte	0	2 (1.0)	7** (1.1)	8** (1.4)

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

Kidney: The incidence of nephropathy was slightly increased in 800 mg/L males and 400 and 800 mg/L females (Tables 21, B6, and B8). The increases were not statistically significant. These lesions were minimal to moderate in severity. The incidences of renal tubule degeneration and renal cell hypertrophy were significantly increased in the 800 mg/L groups of males and females (Tables 21, B6, and B8).

Epididymis: Incidences of tubule degeneration were significantly increased in the 800 mg/L males (Tables 21 and B6). Epididymal tubules with degeneration had reduced numbers of spermatozoa and increased numbers of sloughed cells or had eosinophilic fluid completely devoid of cells.

Testes: Absolute testis weights were significantly decreased in 800 mg/L males when compared to controls (Table F4). Incidences of germinal epithelium degeneration increased with increasing exposure concentration. Significantly increased incidences occurred in the 800 mg/L groups (Tables 21 and B6). Microscopically, the degeneration was similar to that observed in the dermal study at 39 weeks. The incidence of interstitial cell hyperplasia was increased in the 800 mg/L group. The increase was not statistically significant.

Pituitary Gland: The incidence of pars distalis hypertrophy was significantly increased in 800 mg/L females and was characterized by an increase in the size of chromophobes (Tables 21 and B8).

Thymus: The incidence of atrophy was significantly increased in females exposed to 800 mg/L (0 mg/L, 2/10; 80 mg/L, 5/10; 400 mg/L, 6/10; 800 mg/L, 9/10; Table B8). The atrophy has an unknown relationship to sodium bromate exposure.

Forestomach: Combined incidences of multiple and single squamous cell papillomas of the forestomach were decreased in the 400 and 800 mg/L groups of male mice (4/10, 4/10, 1/10, 1/10; Table B7); the decreases were not significant. Combined incidences of multiple and single squamous cell papillomas of the forestomach were slightly increased in the 80 and 400 mg/L groups of female mice (1/10, 4/10, 3/10, 1/10; Table B5). The increases were not significant. The incidence of hyperkeratosis of the forestomach epithelium was significantly increased in 800 mg/L females (Tables 21 and B8). This increase was not accompanied by increases in epithelial hyperplasia or papillomas.

TABLE 21
Incidences of Selected Nonneoplastic Lesions in Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L		80 mg/L		400 mg/L		800 mg/L	
Male								
Kidney[a]	10		10		10		10	
Nephropathy	7		6		7		10	
Renal Tubule, Degeneration[b]	0		0		1	(3.0)[c]	8**	(3.0)
Renal Tubule, Hypertrophy	0		0		1	(1.0)	6**	(1.3)
Epididymis	10		10		10		10	
Degeneration	1	(4.0)	1	(4.0)	0		7**	(3.3)
Testes	10		10		10		10	
Germinal Epithelium, Degeneration	0		0		3	(2.0)	8**	(2.9)
Interstitial Cell, Hyperplasia	0		0		0		3	(1.3)
Female								
Kidney	10		10		10		10	
Nephropathy	6		6		8		8	
Renal Tubule, Degeneration	0		0		0		7**	(2.3)
Renal Tubule, Hypertrophy	0		0		2	(1.0)	5*	(1.6)
Pituitary Gland	10		10		9		10	
Pars Distalis, Hypertrophy	0		0		2	(1.0)	6**	(2.2)
Forestomach	10		10		10		10	
Epithelium, Hyperkeratosis	1	(2.0)	2	(1.0)	1	(1.0)	7**	(1.3)

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

27-Week Drinking Water Study in p53 Haploinsufficient Mice

Survival

Estimates of 27-week survival probabilities for male and female mice are shown in Table 22. Survival of all exposed groups was similar to that of the control groups.

Body Weights and Clinical Findings

Mean body weights of male mice were generally similar to those of the controls throughout the study. Mean body weights of 400 and 800 mg/L female mice were less than those of the control group after week 8 (Figure 5; Tables 23 and 24). Water consumption by exposed mice was generally similar to that by controls throughout the study (Tables H5 and H6). Drinking water concentrations of 80, 400, and 800 mg/L resulted in average daily doses of approximately 8, 39, and 74 mg/kg to male mice and 13, 72, and 136 mg/kg to female mice. There were no clinical findings attributed to sodium bromate administration.

Table 22
Survival of p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Animals initially in study	15	15	15	15
Moribund	0	1	1	0
Natural deaths	1	0	0	1
Animals surviving to study termination	14	14	14	14
Percent probability of survival at end of study[a]	93	93	93	93
Mean survival (days)[b]	183	181	180	179
Survival analysis[c]	P=1.000	P=1.000	P=1.000	P=1.000
Female				
Animals initially in study	15	15	15	15
Natural deaths	1	0	0	1
Animals surviving to study termination	14	15	15	14
Percent probability of survival at end of study	93	100	100	93
Mean survival (days)	183	185	185	181
Survival analysis	P=1.000	P=1.000N	P=1.000N	P=1.000

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] 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 exposure group is indicated by **N**.

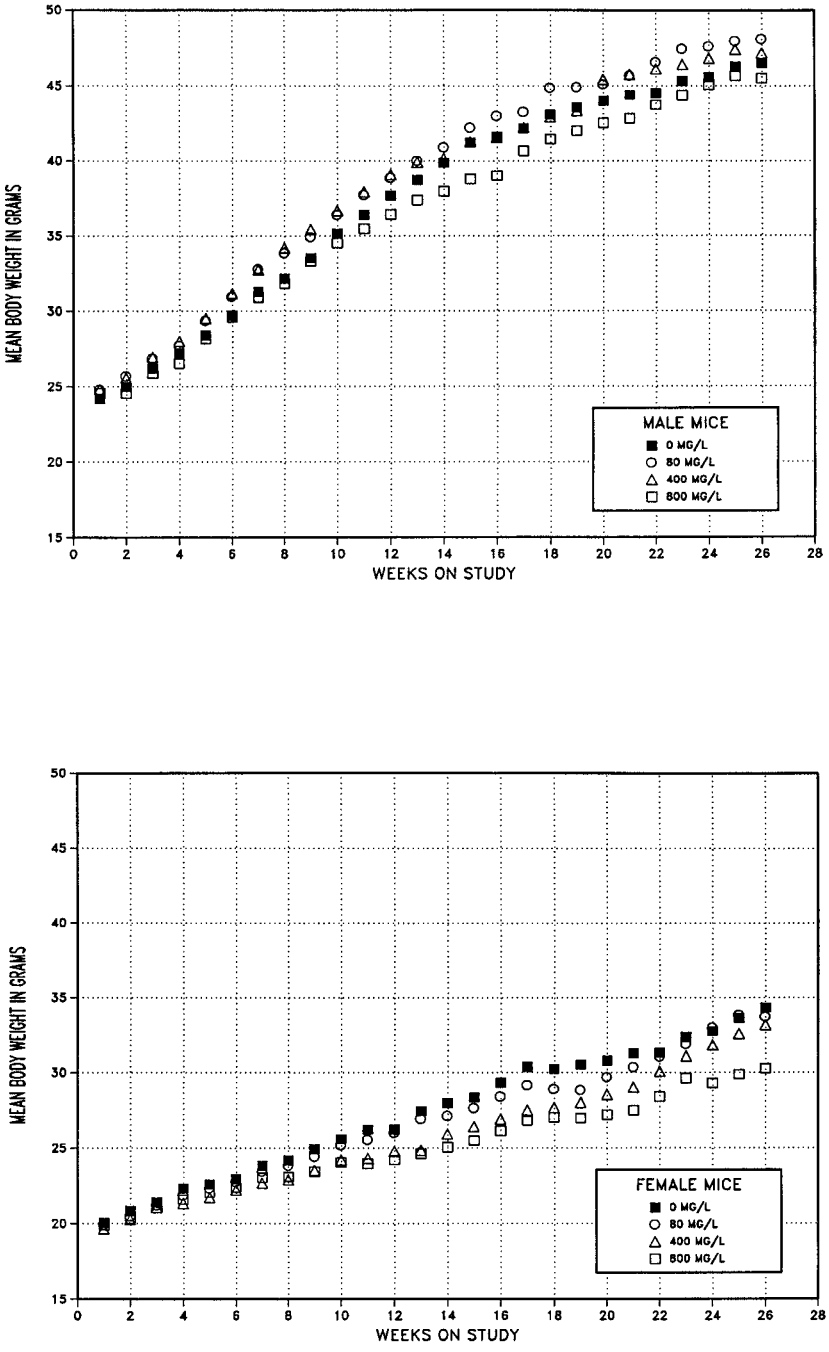


FIGURE 5
Growth Curves for Male and Female p53 Haploinsufficient Mice Exposed to Sodium Bromate in Drinking Water for 27 Weeks

TABLE 23
Mean Body Weights and Survival of Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.2	15	24.8	103	15	24.8	103	15	24.6	102	15
2	25.0	15	25.7	103	15	25.6	102	15	24.6	98	15
3	26.2	15	26.8	102	15	27.0	103	15	25.9	99	15
4	27.2	15	27.7	102	15	28.0	103	15	26.5	97	15
5	28.4	15	29.3	103	15	29.5	104	15	28.2	99	15
6	29.7	15	30.9	104	15	31.1	105	15	29.6	100	15
7	31.3	15	32.8	105	15	32.7	105	15	30.9	99	15
8	32.2	15	33.8	105	15	34.2	106	15	31.8	99	15
9	33.5	15	34.9	104	15	35.4	106	15	33.3	99	15
10	35.1	15	36.4	104	15	36.7	105	15	34.5	98	15
11	36.4	15	37.7	104	15	37.9	104	15	35.5	98	15
12	37.7	15	38.9	103	15	39.1	104	15	36.4	97	15
13	38.7	15	40.0	103	15	39.9	103	15	37.4	97	15
14	39.9	15	40.9	103	15	40.1	101	15	38.0	95	15
15	41.2	15	42.2	102	15	41.3	100	15	38.8	94	15
16	41.6	15	43.0	103	15	41.6	100	15	39.0	94	15
17	42.2	15	43.3	103	15	42.2	100	15	40.7	96	14
18	43.1	15	44.9	104	15	42.9	100	15	41.5	96	14
19	43.6	15	44.9	103	15	43.3	99	15	42.0	96	14
20	44.0	15	45.1	103	15	45.4	103	14	42.6	97	14
21	44.4	15	45.7	103	15	45.8	103	14	42.8	96	14
22	44.5	15	46.6	105	14	46.1	104	14	43.7	98	14
23	45.3	15	47.4	105	14	46.4	102	14	44.4	98	14
24	45.6	15	47.6	104	14	46.8	103	14	45.1	99	14
25	46.3	15	48.0	104	14	47.4	102	14	45.7	99	14
26	46.5	14	48.1	103	14	47.2	102	14	45.5	98	14
Mean for weeks											
1-13	31.2		32.3	103		32.5	104		30.7	98	
14-26	43.7		45.2	103		44.3	101		42.3	97	

TABLE 24
Mean Body Weights and Survival of Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.1	15	19.9	99	15	19.6	98	15	19.9	99	15
2	20.8	15	20.5	99	15	20.3	98	15	20.4	98	15
3	21.4	15	21.2	99	15	21.1	99	15	21.0	98	15
4	22.3	15	21.9	98	15	21.3	96	15	21.6	97	15
5	22.6	15	22.3	99	15	21.7	96	15	22.1	98	15
6	23.0	15	22.8	99	15	22.2	97	15	22.4	97	15
7	23.8	15	23.4	98	15	22.7	95	15	23.1	97	15
8	24.2	15	23.8	98	15	22.9	95	15	23.1	96	15
9	24.9	15	24.4	98	15	23.5	94	15	23.4	94	15
10	25.6	15	25.2	98	15	24.2	95	15	24.0	94	15
11	26.2	15	25.5	97	15	24.3	93	15	24.0	92	15
12	26.2	15	26.0	99	15	24.8	95	15	24.2	92	15
13	27.4	15	26.9	98	15	24.8	91	15	24.6	90	15
14	28.0	15	27.1	97	15	25.9	93	15	25.1	90	15
15	28.4	15	27.6	97	15	26.4	93	15	25.5	90	15
16	29.3	15	28.4	97	15	26.9	92	15	26.1	89	15
17	30.4	15	29.2	96	15	27.5	91	15	26.8	88	15
18	30.2	15	28.9	96	15	27.7	92	15	27.0	89	15
19	30.5	15	28.8	94	15	28.0	92	15	27.0	89	14
20	30.8	15	29.7	96	15	28.5	93	15	27.2	88	14
21	31.3	15	30.3	97	15	29.0	93	15	27.5	88	14
22	31.3	15	31.0	99	15	30.1	96	15	28.4	91	14
23	32.4	14	31.9	99	15	31.1	96	15	29.6	91	14
24	32.8	14	33.0	101	15	31.8	97	15	29.3	89	14
25	33.6	14	33.8	101	15	32.6	97	15	29.9	89	14
26	34.3	14	33.7	98	15	33.2	97	15	30.3	88	14
Mean for weeks											
1-13	23.7		23.4	99		22.6	95		22.6	95	
14-26	31.0		30.3	98		29.1	94		27.7	89	

Hematology

In contrast to the results of the studies conducted in Tg.AC hemizygous mice, the erythron in p53 haploinsufficient mice demonstrated minimal (less than or equal to 5%) increases in erythrocyte counts in 400 mg/L female and 800 mg/L male and female mice (Tables 25 and E3). Similar to the observations with Tg.AC mice, minimal (4% or less) decreases in mean cell hemoglobin were observed in 800 mg/L male and female p53 haploinsufficient mice and a slight (37%) increase in reticulocyte counts was observed in 800 mg/L males. The biological significance of these erythron changes was unknown but indicates that the two mouse strains responded differently when administered the same concentrations of sodium bromate in drinking water.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions. There were no neoplasms or nonneoplastic lesions in either male or female p53 haploinsufficient mice that were attributed to exposure to sodium bromate (Tables C1, C2, C3 and C4).

TABLE 25
Selected Hematology Data for p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	14	14	13	14
Hematocrit (%)	46.7 ± 0.4	47.5 ± 0.2	46.4 ± 0.6	47.5 ± 0.7
Hemoglobin (g/dL)	15.2 ± 0.1	15.4 ± 0.1	14.9 ± 0.2	15.2 ± 0.2
Erythrocytes (10^6/µL)	10.41 ± 0.13	10.52 ± 0.08	10.33 ± 0.12	10.87 ± 0.19*
Reticulocytes (10^6/µL)	0.15 ± 0.01	0.16 ± 0.01	0.17 ± 0.02	0.20 ± 0.01*
Mean cell volume (fL)	44.9 ± 0.3	45.2 ± 0.2	44.9 ± 0.2	43.8 ± 0.3
Mean cell hemoglobin (pg)	14.6 ± 0.1	14.6 ± 0.1	14.4 ± 0.1	14.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.5 ± 0.1	32.1 ± 0.1	32.0 ± 0.1**
Female				
n	14	15	15	14
Hematocrit (%)	46.1 ± 0.4	47.2 ± 0.4	48.0 ± 0.6*	47.0 ± 0.4
Hemoglobin (g/dL)	14.8 ± 0.1	15.2 ± 0.1	15.3 ± 0.2*	15.0 ± 0.2
Erythrocytes (10^6/µL)	10.25 ± 0.09	10.49 ± 0.08	10.76 ± 0.13**	10.72 ± 0.09**
Reticulocytes (10^6/µL)	0.20 ± 0.01	0.18 ± 0.01	0.17 ± 0.01	0.20 ± 0.01
Mean cell volume (fL)	45.0 ± 0.2	44.9 ± 0.1	44.7 ± 0.2	43.9 ± 0.2**
Mean cell hemoglobin (pg)	14.4 ± 0.1	14.5 ± 0.1	14.3 ± 0.0	14.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.1	32.3 ± 0.1	32.0 ± 0.1	31.8 ± 0.1

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

43-Week Drinking Water Study

Survival

Estimates of 43-week survival probabilities for male and female mice are shown in Table 26. Survival of all exposed groups was similar to that of the control groups.

Body Weights and Clinical Findings

Mean body weights of male mice were generally similar to those of the controls throughout the study. Mean body weights of 400 and 800 mg/L females were less than those of the controls beginning at weeks 11 and 16 of the study, respectively (Tables 27 and 28; Figure 6). Water consumption by exposed mice was generally similar to that by controls throughout the study (Tables H7 and H8). Drinking water concentrations of 80, 400, and 800 mg/L resulted in average daily doses of approximately 7, 37, and 65 mg/kg to male mice and 11, 58, and 107 mg/kg to female mice. There were no clinical findings attributed to the administration of sodium bromate.

Table 26
Survival of p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
Animals initially in study	10	10	10	10
Moribund	1	2	0	0
Natural deaths	0	0	2	1
Animals surviving to study termination	9	8	8	9
Percent probability of survival at end of study[a]	90	80	80	90
Mean survival (days)[b]	293	284	289	288
Survival analysis[c]	P=1.000N	P=0.924	P=0.976	P=1.000
Female				
Animals initially in study	10	10	10	10
Moribund	0	1	0	0
Natural death	1	0	0	0
Animals surviving to study termination	9	9	10	10
Percent probability of survival at end of study	90	90	100	100
Mean survival (days)	294	293	295	295
Survival analysis	P=0.412N	P=1.000	P=1.000N	P=1.000N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[c] 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 exposure group is indicated by **N**.

TABLE 27
Mean Body Weights and Survival of Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.8	10	24.6	99	10	25.2	102	10	24.7	100	10
2	25.6	10	25.4	99	10	25.9	101	10	24.5	96	10
3	27.2	10	26.8	99	10	27.3	100	10	26.2	96	10
4	28.1	10	27.5	98	10	28.4	101	10	27.3	97	10
5	29.2	10	28.7	98	10	29.5	101	10	28.5	98	10
6	30.8	10	29.8	97	10	30.7	100	10	29.8	97	10
7	32.7	10	31.8	97	10	32.7	100	10	31.8	97	10
8	33.7	10	33.0	98	10	33.9	101	10	32.8	97	10
9	34.7	10	33.8	97	10	33.3	96	10	33.6	97	10
10	35.9	10	35.3	98	10	35.0	98	10	34.6	96	10
11	37.2	10	36.7	99	10	36.7	99	10	35.2	95	10
12	38.6	10	36.7	95	10	37.5	97	10	36.2	94	10
13	39.9	10	38.6	97	10	39.0	98	10	37.3	94	10
14	40.6	10	40.0	99	10	40.0	99	10	38.3	94	10
15	42.0	10	41.1	98	10	41.0	98	10	39.5	94	10
16	42.5	10	42.0	99	10	41.7	98	10	40.0	94	10
17	43.6	10	42.8	98	10	42.4	97	10	40.5	93	10
18	44.3	10	44.0	99	10	43.0	97	10	41.3	93	10
19	45.3	10	44.8	99	10	43.9	97	10	42.2	93	10
20	45.8	10	45.1	99	10	44.3	97	10	43.0	94	10
21	46.3	10	45.8	99	10	44.9	97	10	43.7	94	10
22	46.7	10	46.3	99	10	45.3	97	10	44.1	94	10
23	46.8	10	45.9	98	10	46.0	98	10	44.8	96	10
25	47.5	10	47.7	100	10	47.3	100	10	46.4	98	10
26	48.4	10	47.3	98	10	48.0	99	10	47.2	98	10
27	48.1	10	48.1	100	10	47.8	99	10	46.7	97	10
28	49.5	10	49.3	100	10	48.9	99	10	47.6	96	10
29	49.3	10	49.0	99	10	48.9	99	10	47.9	97	10
30	49.5	10	48.4	98	10	49.0	99	10	48.2	97	10
31	49.8	10	47.7	96	10	49.5	99	10	48.7	98	10
32	50.1	10	49.8	99	9	48.8	97	10	47.2	94	10
33	50.4	10	50.2	100	9	49.6	98	10	48.6	96	9
34	50.1	10	50.5	101	9	48.9	98	10	48.5	97	9
35	49.2	10	50.4	102	9	49.5	101	10	48.9	99	9
36	49.6	10	50.8	102	9	50.1	101	9	49.5	100	9
37	50.4	10	50.6	100	9	50.3	100	9	50.2	100	9
38	50.2	10	51.3	102	8	50.8	101	9	50.5	101	9
39	50.2	10	51.4	102	8	51.0	102	9	50.5	101	9
40	50.0	10	52.1	104	8	51.5	103	9	51.2	102	9
41	51.8	9	52.6	102	8	50.8	98	9	51.7	100	9
42	51.4	9	52.5	102	8	50.9	99	8	51.2	100	9
Mean for weeks											
1-13	32.2		31.4	98		31.9	99		31.0	96	
14-42	47.8		47.8	100		47.3	99		46.4	97	

TABLE 28
Mean Body Weights and Survival of Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

Weeks on Study	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.6	10	20.0	102	10	19.7	101	10	19.8	101	10
2	20.5	10	20.4	100	10	20.0	98	10	19.8	97	10
3	21.2	10	21.6	102	10	20.7	98	10	21.1	100	10
4	21.9	10	22.2	101	10	21.6	99	10	21.4	98	10
5	22.1	10	23.0	104	10	22.0	100	10	22.3	101	10
6	22.5	10	23.4	104	10	22.0	98	10	22.2	99	10
7	23.1	10	23.9	104	10	22.4	97	10	23.0	100	10
8	23.6	10	24.0	102	10	22.5	95	10	23.2	98	10
9	23.4	10	24.4	104	10	22.7	97	10	23.4	100	10
10	24.2	10	24.6	102	10	23.3	96	10	23.9	99	10
11	24.9	10	25.3	102	10	23.4	94	10	24.5	98	10
12	25.7	10	25.9	101	10	23.8	93	10	24.7	96	10
13	26.4	10	27.0	102	10	24.7	94	10	25.4	96	10
14	27.0	10	27.3	101	10	24.4	90	10	25.6	95	10
15	27.6	10	27.7	100	10	24.6	89	10	26.1	95	10
16	28.8	10	28.5	99	10	25.3	88	10	26.9	93	10
17	29.7	10	29.3	99	10	25.7	87	10	27.3	92	10
18	30.5	10	30.4	100	10	26.5	87	10	28.3	93	10
19	31.1	10	31.5	101	10	27.1	87	10	28.7	92	10
20	31.7	10	32.5	103	10	27.5	87	10	28.6	90	10
21	32.5	10	33.0	102	10	28.5	88	10	29.3	90	10
22	33.2	10	33.4	101	10	28.3	85	10	29.9	90	10
23	33.8	10	33.3	99	10	29.3	87	10	30.9	91	10
25	35.9	10	35.3	98	10	30.3	84	10	32.0	89	10
26	36.6	10	35.4	97	10	31.5	86	10	33.1	90	10
27	37.1	10	37.0	100	10	31.9	86	10	33.6	91	10
28	38.9	10	38.6	99	10	33.4	86	10	35.0	90	10
29	38.5	10	38.8	101	10	33.5	87	10	35.3	92	10
30	39.0	10	39.5	101	10	33.1	85	10	36.1	93	10
31	39.8	10	40.2	101	10	33.5	84	10	36.8	93	10
32	40.7	10	40.5	100	10	34.9	86	10	37.0	91	10
33	41.3	10	41.1	100	10	35.3	86	10	36.2	88	10
34	42.2	10	42.2	100	10	35.0	83	10	37.6	89	10
35	42.4	10	42.7	101	10	35.9	85	10	38.0	90	10
36	43.4	10	43.5	100	10	36.8	85	10	39.0	90	10
37	44.5	10	44.5	100	10	37.9	85	10	39.5	89	10
38	45.2	10	44.0	97	10	37.6	83	10	40.5	90	10
39	44.6	10	44.3	99	10	37.9	85	10	40.8	92	10
40	44.1	10	44.4	101	10	38.9	88	10	41.5	94	10
41	45.0	10	46.1	102	9	38.9	86	10	42.2	94	10
42	47.4	9	46.1	97	9	38.6	81	10	42.1	89	10
Mean for weeks											
1-13	23.0		23.5	102		22.2	97		22.7	99	
14-42	37.6		37.5	100		32.2	86		34.2	91	

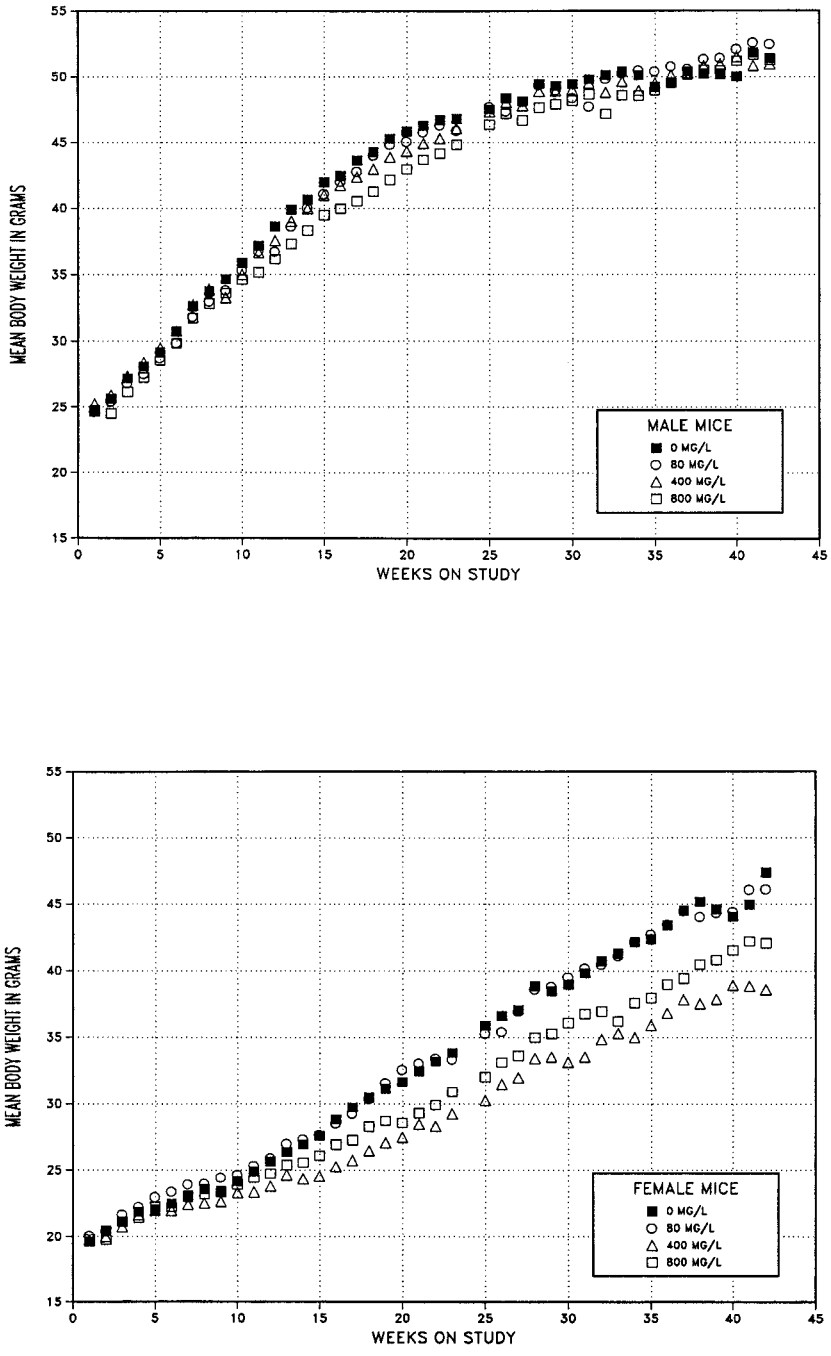


FIGURE 6
Growth Curves for Male and Female p53 Haploinsufficient Mice Exposed to Sodium Bromate in Drinking Water for 43 Weeks

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions. No treatment-related changes in the incidences of neoplasms or nonneoplastic lesions were observed in either male or female p53 haploinsufficient mice (Tables C5, C6, C7, and C8).

GENETIC TOXICOLOGY

Three independent tests for micronucleus induction by sodium bromate were conducted using two strains of transgenic mice. In each test, male and female mice were treated for a period of 26 (dermal) or 27 (drinking water) weeks; at the end of the treatment period, peripheral blood normochromatic (mature) erythrocytes were analyzed for frequency of micronucleated cells. Tg.AC hemizygous mice were dosed by dermal application (Table D1) or exposed via drinking water (Table D2); p53 haploinsufficient mice were exposed through drinking water (Table D3). Results of all three tests were positive in both male and female mice, and were based both on a significant trend as well as significant pairwise comparisons between individual treatment groups and the concurrent control. From the data, it appears that the Tg.AC hemizygous mice were more responsive than the p53 haploinsufficient mice to induction of micronuclei by sodium bromate, particularly if the same route (drinking water) is compared. Significant increases in the percentage of polychromatic erythrocytes among total erythrocytes were observed in male and female Tg.AC hemizygous mice exposed via drinking water and in male Tg.AC hemizygous mice dosed dermally with sodium bromate. No significant alterations in the percentage of polychromatic erythrocytes were seen in female Tg.AC hemizygous mice treated by the dermal route or in male or female p53 haploinsufficient mice.

DISCUSSION AND CONCLUSIONS

Sodium bromate is a drinking water disinfection by-product (DBP) formed during the ozonation of source water containing bromide. It was nominated for toxicity and carcinogenicity studies in genetically modified mouse models by the United States Environmental Protection Agency and the National Institute of Environmental Health Sciences to determine whether transgenic mouse models were effective at determining the potential hazards of DBPs. Male and female Tg.AC hemizygous and p53 haploinsufficient mice were evaluated as models to identify DBPs for carcinogenic potential. The combination of Tg.AC hemizygous mice and p53 haploinsufficient mice has been suggested as an effective means of identifying chemical carcinogens and assessing potential risk (Tennant *et al*., 1995). Tg.AC hemizygous mice were reported to respond to tumor promoters, mutagenic chemicals, and non-mutagenic chemicals while p53 haploinsufficient mice responded to mutagenic chemicals within 6 months, allowing the testing of more chemicals within a shorter period of time (Tennant *et al*., 1995). Sodium bromate was evaluated by the drinking water route because this was the most likely route of human exposure. Dermal studies were included for the Tg.AC hemizygous mice since it was reported that tumors usually occurred within 10 weeks of initiation of exposure (Tennant *et al*., 1995) and because humans are exposed dermally to DBPs through showering and bathing.

There were no increased incidences of neoplasms in male or female Tg.AC hemizygous or p53 haploinsufficient mice exposed to sodium bromate by the dermal or drinking water routes. Dermal administration of sodium bromate for 26 or 39 weeks did not result in significant treatment-related increases in neoplasms or nonneoplastic lesions of the skin of either male or female Tg.AC hemizygous mice. This is consistent with a study in the literature that demonstrated that potassium bromate was not a skin carcinogen or a promoter of skin cancer in Sencar mice (Kurokawa *et al*., 1984). Sodium bromate did not cause overt toxicity in Tg.AC hemizygous mice following dermal administration. Dermal penetration and subsequent systemic circulation of sodium bromate has been reported to be very low (CIREP, 1994). In the Tg.AC hemizygous mouse dermal study, nonneoplastic lesions attributed to sodium bromate were found in the kidneys, thyroid gland, spleen, and testes. Similar lesions were found in the kidneys, thyroid gland, and testes of Tg.AC hemizygous mice given sodium bromate in the drinking water. The systemic dose of sodium bromate was probably increased following dermal administration with oral consumption of sodium bromate during grooming, and it is likely that the systemic effects resulted from the oral exposure. The dose for the dermal administration of sodium bromate was higher than the dose for the drinking water studies based on consumption and formulation concentration data. For example, the dermal dose groups received 64, 128, and 256 mg/kg per day, whereas the exposure levels for the drinking water studies were approximately 13 to 15 mg/kg per day in the 80 mg/L group, 63 to 72 mg/kg per day in the 400 mg/L group, and 129 to 148 mg/kg per day in the 800 mg/L group. Although the exposure levels differed somewhat, the type and incidence of the effects suggested that the internal doses were similar between the two routes of exposure.

Nonneoplastic lesions attributed to sodium bromate exposure from the drinking water were found in the kidneys, thyroid and pituitary glands, and the testes/epididymides of the Tg.AC hemizygous mice. No neoplasms attributed to sodium bromate exposure were observed in male or female Tg.AC hemizygous mice. These results are in contrast to numerous traditional carcinogenicity studies that demonstrate that potassium bromate is a rodent carcinogen when administered in drinking water. Potassium bromate increased the incidence of renal tumors in male F344/N rats as well as the incidences of mesothelioma and thyroid gland tumors (DeAngelo *et al*., 1998). Although kidney tumors following potassium bromate exposure have been shown to be more prevalent in rats than mice, DeAngelo *et al*. (1998) also observed renal tumors in $B6C3F_1$ mice treated with potassium bromate in the drinking water at concentrations ranging from 0.08 to 0.8 g/L for up to 100 weeks. An increase in renal tumors was observed at the low concentration but not the mid or high concentrations (DeAngelo *et al*., 1998). Female $B6C3F_1$ mice

treated for 78 weeks with 500 or 1,000 ppm of potassium bromate in the drinking water did not develop renal tumors (Kurokawa *et al*., 1986b). However, renal tumors were found in male $B6C3F_1$, BDF_1, and CDF_1 mice after exposure to 750 ppm potassium bromate in drinking water for 88 weeks (Kurokawa *et al*., 1990). Although these incidences were not statistically significant, the authors concluded that there was a potential for potassium bromate to induce renal cell tumors in mice. Nephropathy was the only renal abnormality attributed to sodium bromate exposure in the present transgenic mouse studies. A dose-related increase in the severity of chronic progressive nephropathy was associated with dysplastic foci and tumors in rats treated with potassium bromate for up to 2 years (Kurokawa *et al*., 1983a, 1986a). In contrast, DeAngelo *et al*. (1998) did not observe any association between potassium bromate treatment and nephropathy.

There have been several studies on the mechanism of potassium bromate induced renal carcinogenesis. The development of tumors from chronic exposure to potassium bromate is thought to result from oxidative DNA damage following bromate metabolism and subsequent lipid peroxidation (Kurokawa *et al*., 1990; Sai *et al*., 1991, 1992b; Umemura *et al*., 1998). Data in the literature indicate that the species differences observed in the induction of renal cell tumors are correlated with different levels of lipid peroxidation. Lipid peroxide levels were significantly increased in a dose- and time-dependent manner in the kidneys of male F344 rats after intravenous administration of potassium bromate but not in CDF_1, $B6C3F_1$, or BDF_1 mice (Kurokawa *et al*., 1987b). Bromate causes oxidative DNA damage as evidenced by the formation of 8-hydroxydeoxyguanosine (8-OH-dG) in kidney DNA. Kurokawa *et al*. (1990) have demonstrated a positive correlation between the formation of 8-OH-dG in rat kidney DNA and potassium bromate induced carcinogenesis. Incubation of bromate directly with DNA *in vitro* did not result in 8-OH-dG production indicating that bromate needs to undergo cellular metabolism to cause DNA damage (Kurokawa *et al*., 1990).

It is possible that the duration of treatment in the present studies was not long enough to detect renal tumors in the Tg.AC hemizygous mouse. Other chemicals that cause renal cancer in 2-year rodent studies have also failed to cause tumors in the Tg.AC hemizygous model. Three chemicals that caused kidney tumors in male $B6C3F_1$ mice and another chemical that produced kidney tumors in male F344 rats did not produce tumors in Tg.AC mice when administered dermally (Spalding *et al*., 2000). Chloroprene exposure caused increased incidences of renal tubule adenomas in male and female F344/N rats and male $B6C3F_1$ mice but failed to cause tumors in Tg.AC hemizygous mice after inhalation exposure (NTP, 1998; Pritchard *et al*., 2003). Male $B6C3F_1$ mice given bromodichloromethane, another drinking water disinfection by-product, by gavage for 2 years had increased incidences of kidney adenomas and adenocarcinomas (NTP, 1987). However, the Tg.AC hemizygous mouse failed to respond to doses of bromodichloromethane that exceeded those in the 2-year study (NTP, 2006a). These data suggest that the Tg.AC hemizygous model is not responsive to rodent renal carcinogens. In a review of 38 chemicals evaluated by NIEHS/NTP in genetically modified mice, 11 (20%) of the chemicals that produced tumors in the 2-year assays were not detected as carcinogens in the transgenic mouse models (Bucher, 1998). A larger review found that the Tg.AC hemizygous model has about 77% accuracy for detecting potential carcinogens (Pritchard *et al*., 2003).

Nonneoplastic lesions in the thyroid gland of Tg.AC hemizygous mice included follicular secretory depletion, follicular cell hypertrophy, and lymphocytic infiltration. These findings were observed in male and female Tg.AC hemizygous mice exposed to sodium bromate dermally or in drinking water. While no thyroid gland lesions were found in the 2-year potassium bromate drinking water study using $B6C3F_1$ mice, potassium bromate is carcinogenic in the F344/N rat thyroid, producing thyroid gland follicular adenomas and carcinomas at water concentrations as low as 0.02 g/L (DeAngelo *et al*., 1998). Bromate is similar in structure to chlorate and perchlorate. Both are thyroid gland toxicants and induce follicular cell tumors in rats (Hooth *et al*., 2001; NTP, 2005a). Most chemically induced thyroid gland neoplasms appear to result from direct interference with the synthesis of thyroid hormones, resulting in a decreased circulating level of T_3 or T_4 with subsequent elevated thyroid stimulating hormone (TSH) secretion and stimulation of thyroid cell proliferation. Follicular cell proliferation often follows a progression from hyperplasia to neoplasia (Hardisty and Boorman, 1990). The mechanism by which potassium bromate induced thyroid gland tumors is not known. Bromide binds to the sodium-iodide symporter of the thyroid gland with low affinity (Van Sande *et al*., 2003). High levels of bromide result in a decrease in iodide accumulation in the thyroid gland

and a rise in iodide excretion by the kidneys, leading to decreased thyroid hormone synthesis and stimulation of thyroid gland cell proliferation (Pavelka, 2004).

The effect of bromate on the thyroid gland may explain the increased incidence of pars distalis hypertrophy in female Tg.AC hemizygous mice treated with 800 mg/L sodium bromate in the drinking water for 27 or 43 weeks. Treatment-related lesions of the pituitary gland in mice are uncommon and are usually a secondary effect of toxicity involving a target endocrine organ (Mahler and Elwell, 1999). Induction of par distalis lesions secondary to proliferative lesions of the thyroid follicular cells have been observed in previous chronic rodent studies (Mahler and Elwell, 1999). These findings are attributed to a reduction of circulating T_3 and/or T_4 which stimulates cells by a feedback mechanism in the hypothalamus and pars distalis of the pituitary gland to increase the production of corresponding releasing factors and stimulating hormones (Mahler and Elwell, 1999). Thus, the effects of sodium bromate on the pituitary gland may be secondary to the changes that occurred in the thyroid gland.

Absolute testis weights were significantly decreased in Tg.AC hemizygous males exposed to sodium bromate dermally for 39 weeks or in the drinking water for 43 weeks. The incidences of germinal epithelium degeneration increased with increasing exposure concentration. At 43 weeks, the incidences of epididymal tubule degeneration were significantly increased in the 800 mg/L males. The tubules with degeneration had reduced numbers of spermatozoa. These observations are consistent with previous NTP reproductive toxicity studies demonstrating decreases in sperm density in male Sprague-Dawley rats exposed to sodium bromate in the drinking water (NTP, 1996; NTP, 2001). The mechanism of this effect is not known.

Clinical pathology parameters indicated that sodium bromate had minimal treatment-related effects on the red blood cells. Tg.AC hemizygous mice exposed to sodium bromate dermally or in drinking water exhibited decreases in erythron (hemoglobin, hematocrit, and red cell counts), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC), which may indicate a weak depressive effect on bone marrow red cell production. An apparent regenerative-type response was indicated by an increase in reticulocyte counts. Increased hematopoiesis was also indicated by significant increases in the percentage of polychromatic erythrocytes in Tg.AC hemizygous mice treated with sodium bromate. The incidences of splenic hematopoietic cell proliferation increased with increasing dose, and significant increases occurred in female Tg.AC hemizygous mice dosed dermally with 128 and 256 mg/kg sodium bromate for 26 weeks. With the exception of a small decrease in MCH, hematology parameters were not generally altered in p53 haploinsufficient mice. For the Tg.AC hemizygous mice, there appeared to be a very mild treatment-related anemia that was accompanied by a regenerative response. The mechanism for the anemia is unknown; however, the bone marrow and the spleen were able to respond to the lowered erythron.

Significant dose-related increases in micronucleated erythrocytes, indicative of induced chromosomal damage in the form of breaks or chromosome loss, were observed in all three experimental groups of mice (Appendix D). Increases in the percentage of polychromatic erythrocytes (PCEs) in peripheral blood, paralleling the observations of regenerative responses to the erythron decreases in Tg.AC hemizygous mice, were also observed. A significant increase in the percentage of PCEs indicates a stimulation of erythropoiesis and this may be important in interpreting experimental results, particularly weak positive responses in the micronucleus assay, as an enriched PCE population may artificially inflate a weak response. Increased erythropoiesis has been shown to slightly elevate the frequency of micronucleated PCEs as a consequence of accelerated cell division producing an increase in mitotic errors (Hirai *et al*.,1991; Suzuki *et al*., 1989). In this study with sodium bromate, significant increases in micronucleated normochromatic erythrocytes (MN-NCE) were seen in Tg.AC hemizygous mice at doses lower than those that resulted in significant increases in the percent PCEs, and significant increases in MN-NCE were observed in p53 haploinsufficient mice in the absence of any significant alteration in PCE/NCE ratios at any dose level. Thus, it does not appear that stimulation of erythropoiesis alone is responsible for the observed increases in the frequency of micronucleated erythrocytes in Tg.AC hemizygous and p53 haploinsufficient mice.

No neoplastic or nonneoplastic findings were observed in the p53 haploinsufficient mice exposed to sodium bromate in the drinking water. The absence of a carcinogenic response in p53 haploinsufficient mice, in light of the positive micronucleus test results, is surprising because a strong correlation has been reported between positive results in subchronic peripheral blood micronucleus tests and rodent carcinogenicity (Witt *et al*., 2000). Although the number of positive studies from which this

correlation derives is small, additional evidence was provided by Morita *et al*. (1997), who reported a 90.5% correlation between carcinogenic activity in humans and positive results in the rodent micronucleus test when data were corrected for known structure-activity considerations with regard to micronucleus assay sensitivity. In addition, Zeiger (1998) reported a 70% correlation between rodent carcinogenicity and positive results in the mouse bone marrow micronucleus test in an unadjusted dataset of 83 NTP chemicals. Other chemicals, including diisopropylcarbodiimide (NTP, 2006b) and aspartame (NTP, 2005b), have produced significant increases in MN-NCE in the absence of evidence of carcinogenicity in p53 haploinsufficient mice. It is unlikely that the negative response was due to low exposure levels. Based on earlier studies, the concentrations used for exposure in the present study produced renal tumors in rodents, including mice. In addition, the actual exposure levels were similar to the doses used for the Tg.AC mice where minimal toxicity was observed. Therefore, the data indicate that the p53 haploinsufficient mouse was not responsive to sodium bromate exposure even though sodium bromate is genotoxic.

In conclusion, no neoplastic lesions were attributed to sodium bromate, a known rodent carcinogen, in Tg.AC hemizygous and p53 haploinsufficient transgenic mice exposed dermally or through the drinking water. These studies provide evidence that these transgenic mouse models are not a sensitive and rapid means of assessing potential toxicity and carcinogenicity of sodium bromate.

CONCLUSIONS

Under the conditions of these drinking water studies, there was *no evidence of carcinogenic activity** of sodium bromate in male or female p53 haploinsufficient mice exposed to 80, 400, or 800 mg/L for 27 or 43 weeks.

No treatment-related neoplasms were seen in male or female Tg.AC hemizygous mice exposed dermally to 64, 128, or 256 mg sodium bromate/kg body weight for 26 or 39 weeks.

No treatment-related neoplasms were seen in male or female Tg.AC hemizygous mice exposed by drinking water to 80, 400, or 800 mg sodium bromate/L for 27 or 43 weeks.

In drinking water and dermal studies in Tg.AC hemizygous mice there were increased incidences of nonneoplastic lesions in the thyroid gland and kidney.

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

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APPENDIX A
SUMMARY OF LESIONS
IN Tg.AC HEMIZYGOUS MICE
IN THE DERMAL STUDIES
OF SODIUM BROMATE

TABLE A1
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	1		
Natural deaths	1	3	2	
Survivors				
Terminal sacrifice	12	11	13	15
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Stomach, forestomach	(15)	(15)	(15)	(15)
Squamous cell papilloma	1 (7%)	4 (27%)	4 (27%)	3 (20%)
Squamous cell papilloma, multiple	2 (13%)	2 (13%)	2 (13%)	4 (27%)
Tooth	(3)	(1)	(1)	(3)
Odontogenic tumor	3 (100%)	1 (100%)	1 (100%)	3 (100%)
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Adrenal medulla	(15)	(15)	(15)	(15)
Pituitary gland	(15)	(14)	(15)	(15)
Hematopoietic System				
Lymph node		(1)		
Lymph node, mandibular	(15)	(15)	(15)	(15)
Lymph node, mesenteric	(15)	(15)	(15)	(15)
Spleen	(15)	(15)	(15)	(15)
Integumentary System				
Skin	(15)	(15)	(15)	(15)
Squamous cell papilloma	2 (13%)	3 (20%)	1 (7%)	4 (27%)
Squamous cell papilloma, multiple			1 (7%)	
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Systemic Lesions				
Multiple organs[b]	(15)	(15)	(15)	(15)
Leukemia erythrocytic		2 (13%)	1 (7%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	6	9	9	11
Total primary neoplasms	8	12	10	14
Total animals with benign neoplasms	4	8	7	10
Total benign neoplasms	5	9	8	11
Total animals with malignant neoplasms		2	1	
Total malignant neoplasms		2	1	
Total animals with uncertain neoplasms-benign or malignant	3	1	1	3
Total uncertain neoplasms	3	1	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
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	1		
Natural deaths	1	3	2	
Survivors				
Terminal sacrifice	12	11	13	15
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation			1 (7%)	1 (7%)
Inflammation, chronic active	10 (67%)	6 (40%)	9 (60%)	11 (73%)
Hepatocyte, necrosis	1 (7%)	2 (13%)		
Hepatocyte, vacuolization cytoplasmic	6 (40%)	4 (27%)	3 (20%)	6 (40%)
Mesentery		(1)	(1)	
Fat, necrosis		1 (100%)	1 (100%)	
Stomach, forestomach	(15)	(15)	(15)	(15)
Epithelium, hyperplasia	1 (7%)	2 (13%)	1 (7%)	
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Accessory adrenal cortical nodule	1 (7%)			
Hypertrophy	8 (53%)	4 (27%)	1 (7%)	3 (20%)
Subcapsular, hyperplasia			1 (7%)	
Pituitary gland	(15)	(14)	(15)	(15)
Pars distalis, cyst		3 (21%)	4 (27%)	3 (20%)
Pars distalis, hyperplasia			1 (7%)	
Thyroid gland	(15)	(15)	(15)	(15)
Infiltration cellular, lymphocyte			1 (7%)	
Follicle, depletion secretory	7 (47%)	4 (27%)	5 (33%)	11 (73%)
Follicular cell, hypertrophy		7 (47%)	10 (67%)	14 (93%)
Genital System				
Epididymis	(15)	(15)	(15)	(15)
Degeneration	1 (7%)			2 (13%)
Testes	(15)	(15)	(15)	(15)
Cyst	1 (7%)			1 (7%)
Germinal epithelium, degeneration	2 (13%)		2 (13%)	3 (20%)

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

TABLE A2
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Hematopoietic System				
Lymph node, mandibular	(15)	(15)	(15)	(15)
Necrosis, lymphoid	1 (7%)	1 (7%)		
Lymph node, mesenteric	(15)	(15)	(15)	(15)
Necrosis, lymphoid	1 (7%)			
Spleen	(15)	(15)	(15)	(15)
Atrophy	1 (7%)			
Hematopoietic cell proliferation			1 (7%)	2 (13%)
Thymus	(14)	(15)	(15)	(15)
Atrophy	1 (7%)	4 (27%)	1 (7%)	4 (27%)
Cyst	2 (14%)	2 (13%)	2 (13%)	5 (33%)
Ectopic parathyroid gland		1 (7%)		
Ectopic thyroid		1 (7%)		
Integumentary System				
Skin	(15)	(15)	(15)	(15)
Hyperkeratosis	2 (13%)		3 (20%)	4 (27%)
Hyperkeratosis, focal	1 (7%)			
Inflammation, chronic active		1 (7%)		
Epidermis, hyperplasia, focal	3 (20%)	2 (13%)	3 (20%)	4 (27%)
Site of application - epidermis, hyperplasia, focal				1 (7%)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Inflammation, chronic active		1 (7%)		
Pigmentation		1 (7%)		
Thrombosis				1 (7%)
Alveolar epithelium, hyperplasia	1 (7%)			
Alveolus, infiltration cellular, histiocyte		1 (7%)		
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Nephropathy	8 (53%)	8 (53%)	14 (93%)	14 (93%)
Artery, inflammation, chronic active	1 (7%)			
Renal tubule, dilatation	1 (7%)			2 (13%)
Urethra				(1)
Bulbourethral gland, cyst				1 (100%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

TABLE A3
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	4	1	3
Natural deaths	2	1	3	1
Survivors				
Terminal sacrifice	11	10	11	11
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Stomach, forestomach	(15)	(15)	(15)	(15)
Squamous cell papilloma	3 (20%)	3 (20%)	3 (20%)	5 (33%)
Squamous cell papilloma, multiple	3 (20%)	3 (20%)	4 (27%)	3 (20%)
Tooth	(3)	(2)	(5)	(4)
Odontogenic tumor	3 (100%)	2 (100%)	4 (80%)	4 (100%)
Odontogenic tumor, multiple			1 (20%)	
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Adrenal medulla	(15)	(15)	(15)	(15)
Pituitary gland	(15)	(15)	(15)	(15)
Genital System				
Ovary	(15)	(15)	(15)	(15)
Luteoma				1 (7%)
Teratoma malignant				1 (7%)
Uterus	(15)	(15)	(15)	(15)
Hematopoietic System				
Lymph node		(2)		(2)
Lymph node, mandibular	(15)	(14)	(14)	(15)
Lymph node, mesenteric	(14)	(14)	(13)	(15)
Spleen	(15)	(15)	(15)	(15)
Integumentary System				
Skin	(15)	(15)	(15)	(15)
Squamous cell papilloma	2 (13%)	3 (20%)	4 (27%)	5 (33%)
Squamous cell papilloma, multiple	3 (20%)			4 (27%)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Special Senses System				
Eye		(1)		
Squamous cell papilloma		1 (100%)		

TABLE A3
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Systemic Lesions				
Multiple organs[b]	(15)	(15)	(15)	(15)
Leukemia erythrocytic		2 (13%)	1 (7%)	2 (13%)
Lymphoma malignant			1 (7%)	
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	9	12	12	14
Total primary neoplasms	14	14	18	25
Total animals with benign neoplasms	8	9	8	11
Total benign neoplasms	11	10	11	18
Total animals with malignant neoplasms		2	2	3
Total malignant neoplasms		2	2	3
Total animals with uncertain neoplasms-benign or malignant	3	2	5	4
Total uncertain neoplasms	3	2	5	4

[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 A4
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	4	1	3
Natural deaths	2	1	3	1
Survivors				
Terminal sacrifice	11	10	11	11
Animals examined microscopically	15	15	15	15
Alimentary System				
Intestine large, rectum	(1)	(2)	(1)	
Anus, hyperplasia		1 (50%)		
Liver	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation	2 (13%)	2 (13%)	2 (13%)	3 (20%)
Inflammation, chronic active	13 (87%)	12 (80%)	12 (80%)	12 (80%)
Thrombosis				1 (7%)
Hepatocyte, degeneration		1 (7%)		
Hepatocyte, fatty change		1 (7%)		
Hepatocyte, necrosis	1 (7%)	2 (13%)	1 (7%)	1 (7%)
Hepatocyte, vacuolization cytoplasmic	3 (20%)	4 (27%)	3 (20%)	3 (20%)
Salivary glands				(1)
Atrophy				1 (100%)
Inflammation, chronic active				1 (100%)
Stomach, forestomach	(15)	(15)	(15)	(15)
Epithelium, hyperkeratosis	1 (7%)	2 (13%)	1 (7%)	1 (7%)
Epithelium, hyperplasia	2 (13%)	2 (13%)	1 (7%)	2 (13%)
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Accessory adrenal cortical nodule	3 (20%)	3 (20%)	1 (7%)	1 (7%)
Subcapsular, hyperplasia	4 (27%)	3 (20%)	5 (33%)	3 (20%)
Pituitary gland	(15)	(15)	(15)	(15)
Pars distalis, cyst	2 (13%)	1 (7%)	2 (13%)	
Pars intermedia, cyst	1 (7%)			
Thyroid gland	(15)	(15)	(15)	(15)
Ectopic thymus	1 (7%)			
Infiltration cellular, lymphocyte		6 (40%)	3 (20%)	12 (80%)
Follicle, cyst	1 (7%)			1 (7%)
Follicle, depletion secretory	6 (40%)	11 (73%)	13 (87%)	14 (93%)
Follicular cell, hypertrophy	1 (7%)	9 (60%)	12 (80%)	13 (87%)
Genital System				
Ovary	(15)	(15)	(15)	(15)
Atrophy			1 (7%)	
Cyst			1 (7%)	3 (20%)
Hemorrhage			1 (7%)	
Pigmentation			1 (7%)	
Uterus	(15)	(15)	(15)	(15)
Endometrium, hyperplasia, cystic	11 (73%)	9 (60%)	10 (67%)	10 (67%)

[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 Female Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Hematopoietic System				
Lymph node		(2)		(2)
Mediastinal, hyperplasia, lymphoid		1 (50%)		
Lymph node, mandibular	(15)	(14)	(14)	(15)
Hyperplasia, lymphoid	4 (27%)	2 (14%)	2 (14%)	3 (20%)
Lymph node, mesenteric	(14)	(14)	(13)	(15)
Hyperplasia, lymphoid				1 (7%)
Spleen	(15)	(15)	(15)	(15)
Atrophy		1 (7%)	1 (7%)	1 (7%)
Hematopoietic cell proliferation	3 (20%)	5 (33%)	9 (60%)	10 (67%)
Thymus	(15)	(14)	(15)	(15)
Atrophy	1 (7%)	3 (21%)	4 (27%)	2 (13%)
Cyst	2 (13%)	4 (29%)	2 (13%)	3 (20%)
Integumentary System				
Skin	(15)	(15)	(15)	(15)
Hyperkeratosis		1 (7%)		
Inflammation, chronic active		1 (7%)	1 (7%)	1 (7%)
Inflammation, suppurative		1 (7%)		
Ulcer				1 (7%)
Epidermis, hyperplasia, focal	2 (13%)	3 (20%)	3 (20%)	1 (7%)
Musculoskeletal System				
Bone		(1)		
Fracture		1 (100%)		
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Inflammation, chronic active		2 (13%)		
Thrombosis				1 (7%)
Alveolar epithelium, hyperplasia				1 (7%)
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Nephropathy	8 (53%)	7 (47%)	13 (87%)	15 (100%)
Renal tubule, dilatation	1 (7%)			

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Nervous System
Special Senses System

TABLE A5
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1			2
Natural deaths	1	2	2	
Survivors				
Terminal sacrifice	8	8	8	8
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Salivary glands	(2)			
Carcinoma	1 (50%)			
Carcinosarcoma	1 (50%)			
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma	2 (20%)	2 (20%)	1 (10%)	2 (20%)
Squamous cell papilloma, multiple	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Tooth	(2)	(3)	(3)	(2)
Odontogenic tumor	1 (50%)	2 (67%)	3 (100%)	2 (100%)
Odontogenic tumor, multiple	1 (50%)	1 (33%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pituitary gland	(9)	(10)	(10)	(10)
Hematopoietic System				
Spleen	(10)	(10)	(10)	(10)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Keratoacanthoma			1 (10%)	
Squamous cell carcinoma	1 (10%)	1 (10%)		
Squamous cell papilloma	3 (30%)	7 (70%)	4 (40%)	4 (40%)
Squamous cell papilloma, multiple	4 (40%)	2 (20%)	2 (20%)	2 (20%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)	2 (20%)	1 (10%)	1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)

TABLE A5
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia erythrocytic		1 (10%)	1 (10%)	1 (10%)
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	9	10	7	7
Total primary neoplasms	16	19	14	14
Total animals with benign neoplasms	7	9	6	6
Total benign neoplasms	11	14	10	11
Total animals with malignant neoplasms	3	2	1	1
Total malignant neoplasms	3	2	1	1
Total animals with uncertain neoplasms-benign or malignant	2	3	3	2
Total uncertain neoplasms	2	3	3	2

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

TABLE A6
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1			2
Natural deaths	1	2	2	
Survivors				
Terminal sacrifice	8	8	8	8
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation		1 (10%)	1 (10%)	1 (10%)
Inflammation, chronic active	8 (80%)	8 (80%)	6 (60%)	6 (60%)
Necrosis				2 (20%)
Hepatocyte, fatty change	1 (10%)			
Hepatocyte, vacuolization cytoplasmic	5 (50%)	8 (80%)	6 (60%)	2 (20%)
Mesentery	(1)		(2)	
Fat, fibrosis	1 (100%)		1 (50%)	
Fat, inflammation, chronic active	1 (100%)		2 (100%)	
Fat, necrosis	1 (100%)		2 (100%)	
Stomach, forestomach	(10)	(10)	(10)	(10)
Epithelium, hyperkeratosis		2 (20%)		1 (10%)
Epithelium, hyperplasia		2 (20%)		1 (10%)
Tooth	(2)	(3)	(3)	(2)
Abscess, focal				1 (50%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule			2 (20%)	1 (10%)
Hypertrophy	6 (60%)	5 (50%)	6 (60%)	6 (60%)
Pituitary gland	(9)	(10)	(10)	(10)
Pars distalis, cyst	3 (33%)	3 (30%)	1 (10%)	3 (30%)
Thyroid gland	(10)	(10)	(10)	(10)
Infiltration cellular, lymphocyte			2 (20%)	1 (10%)
Follicle, cyst		1 (10%)		
Follicle, depletion secretory	8 (80%)	7 (70%)	9 (90%)	9 (90%)
Follicular cell, hypertrophy		9 (90%)	8 (80%)	8 (80%)
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Cyst			2 (20%)	2 (20%)
Degeneration	1 (10%)	2 (20%)	3 (30%)	5 (50%)
Inflammation, chronic active			3 (30%)	2 (20%)
Testes	(10)	(10)	(10)	(10)
Cyst		1 (10%)	1 (10%)	2 (20%)
Mineralization			1 (10%)	
Bilateral, germinal epithelium, degeneration		1 (10%)	1 (10%)	2 (20%)
Germinal epithelium, degeneration	1 (10%)	2 (20%)	3 (30%)	6 (60%)

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

TABLE A6
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)			3 (30%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	3 (30%)	2 (20%)	2 (20%)	3 (30%)
Hyperplasia, lymphoid				1 (10%)
Thymus	(10)	(10)	(10)	(9)
Atrophy	3 (30%)	2 (20%)	4 (40%)	3 (33%)
Cyst	7 (70%)	1 (10%)		3 (33%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Hyperkeratosis		1 (10%)		1 (10%)
Epidermis, hyperplasia, focal	4 (40%)	2 (20%)	1 (10%)	2 (20%)
Site of application - epidermis, hyperplasia, focal			1 (10%)	1 (10%)
Subcutaneous tissue, inflammation, chronic active	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active		2 (20%)	1 (10%)	1 (10%)
Alveolar epithelium, hyperplasia		1 (10%)		
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization		1 (10%)		
Nephropathy	7 (70%)	10 (100%)	9 (90%)	10 (100%)
Cortex, cyst		3 (30%)	1 (10%)	
Glomerulus, inflammation, membranoproliferative		1 (10%)	1 (10%)	1 (10%)
Papilla, mineralization	1 (10%)			
Pelvis, dilatation				1 (10%)
Renal tubule, hypertrophy				2 (20%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

TABLE A7
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1	1	2	1
Natural deaths	1	2		1
Survivors				
Terminal sacrifice	7	7	8	8
Missing	1			
Animals examined microscopically	9	10	10	10
Alimentary System				
Liver	(9)	(10)	(10)	(10)
Salivary glands	(1)	(1)	(1)	
Carcinoma		1 (100%)	1 (100%)	
Stomach, forestomach	(9)	(10)	(10)	(10)
Squamous cell papilloma	2 (22%)	1 (10%)	4 (40%)	3 (30%)
Squamous cell papilloma, multiple		1 (10%)	3 (30%)	1 (10%)
Tooth	(2)	(4)	(3)	(3)
Odontogenic tumor	2 (100%)	3 (75%)	2 (67%)	3 (100%)
Odontogenic tumor, multiple			1 (33%)	
Genital System				
Ovary	(9)	(10)	(10)	(10)
Hemangioma		1 (10%)		
Luteoma, multiple			1 (10%)	
Teratoma benign	1 (11%)			
Hematopoietic System				
Spleen	(9)	(10)	(10)	(10)
Integumentary System				
Skin	(9)	(10)	(10)	(10)
Squamous cell papilloma	2 (22%)	2 (20%)	3 (30%)	1 (10%)
Squamous cell papilloma, multiple	4 (44%)	3 (30%)	2 (20%)	3 (30%)
Site of application, squamous cell papilloma	1 (11%)			1 (10%)
Respiratory System				
Lung	(9)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma				1 (10%)
Carcinoma, metastatic, Zymbal's gland	1 (11%)			
Special Senses System				
Zymbal's gland	(2)			
Carcinoma	1 (50%)			
Urinary System				
Kidney	(9)	(10)	(10)	(10)

TABLE A7
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Systemic Lesions				
Multiple organs[b]	(9)	(10)	(10)	(10)
Leukemia erythrocytic	1 (11%)			1 (10%)
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Musculoskeletal System				
Nervous System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	7	7	10	9
Total primary neoplasms	14	12	17	14
Total animals with benign neoplasms	6	5	8	8
Total benign neoplasms	10	8	13	10
Total animals with malignant neoplasms	2	1	1	1
Total malignant neoplasms	2	1	1	1
Total animals with metastatic neoplasms	1			
Total metastatic neoplasms	1			
Total animals with uncertain neoplasms-benign or malignant	2	3	3	3
Total uncertain neoplasms	2	3	3	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 A8
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1	1	2	1
Natural deaths	1	2		1
Survivors				
Terminal sacrifice	7	7	8	8
Missing	1			
Animals examined microscopically	9	10	10	10
Alimentary System				
Liver	(9)	(10)	(10)	(10)
Hematopoietic cell proliferation	2 (22%)	2 (20%)	2 (20%)	2 (20%)
Inflammation, chronic active	7 (78%)	9 (90%)	10 (100%)	9 (90%)
Necrosis	2 (22%)	1 (10%)	1 (10%)	2 (20%)
Hepatocyte, fatty change	1 (11%)			
Hepatocyte, vacuolization cytoplasmic	7 (78%)	4 (40%)	7 (70%)	8 (80%)
Stomach, forestomach	(9)	(10)	(10)	(10)
Epithelium, hyperkeratosis	1 (11%)	1 (10%)	2 (20%)	1 (10%)
Epithelium, hyperplasia	1 (11%)	1 (10%)	3 (30%)	2 (20%)
Endocrine System				
Adrenal cortex	(9)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (22%)	2 (20%)	2 (20%)	4 (40%)
Subcapsular, hyperplasia	4 (44%)	7 (70%)	7 (70%)	3 (30%)
Pituitary gland	(9)	(10)	(10)	(10)
Pars distalis, hypertrophy				1 (10%)
Pars distalis, inflammation, chronic active	1 (11%)			
Thyroid gland	(9)	(10)	(10)	(10)
Infiltration cellular, lymphocyte		2 (20%)	5 (50%)	10 (100%)
Follicle, depletion secretory	5 (56%)	8 (80%)	10 (100%)	10 (100%)
Follicular cell, hypertrophy	1 (11%)	9 (90%)	9 (90%)	10 (100%)
Genital System				
Ovary	(9)	(10)	(10)	(10)
Cyst	1 (11%)	4 (40%)	2 (20%)	5 (50%)
Inflammation, chronic active	1 (11%)			1 (10%)
Pigmentation, hemosiderin				1 (10%)
Corpus luteum, degeneration				1 (10%)
Thecal cell, hyperplasia				1 (10%)
Uterus	(9)	(10)	(10)	(10)
Endometrium, hyperplasia, cystic	8 (89%)	7 (70%)	8 (80%)	10 (100%)

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

TABLE A8
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Hematopoietic System				
Lymph node, mandibular	(9)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (11%)	3 (30%)	2 (20%)	2 (20%)
Spleen	(9)	(10)	(10)	(10)
Atrophy	1 (11%)	1 (10%)		
Hematopoietic cell proliferation	3 (33%)	6 (60%)	8 (80%)	8 (80%)
Thymus	(8)	(10)	(10)	(10)
Atrophy	1 (13%)	1 (10%)	2 (20%)	1 (10%)
Cyst		1 (10%)	2 (20%)	5 (50%)
Integumentary System				
Skin	(9)	(10)	(10)	(10)
Inflammation, chronic active			1 (10%)	
Ulcer			1 (10%)	
Epidermis, hyperplasia, focal	2 (22%)	2 (20%)	6 (60%)	3 (30%)
Site of application - dermis, cyst epithelial inclusion				1 (10%)
Site of application - epidermis, hyperplasia			1 (10%)	
Subcutaneous tissue, cyst epithelial inclusion				1 (10%)
Respiratory System				
Lung	(9)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)	1 (10%)	
Metaplasia, osseous				1 (10%)
Perivascular, infiltration cellular, lymphocyte				1 (10%)
Special Senses System				
Eye	(1)			
Cornea, inflammation, chronic active	1 (100%)			
Zymbal's gland	(2)			
Cyst	1 (50%)			
Inflammation, chronic active	1 (50%)			
Urinary System				
Kidney	(9)	(10)	(10)	(10)
Mineralization			1 (10%)	
Nephropathy	5 (56%)	6 (60%)	8 (80%)	10 (100%)
Artery, inflammation, chronic active		1 (10%)		
Cortex, cyst	1 (11%)			
Renal tubule, hypertrophy				4 (40%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System

APPENDIX B
SUMMARY OF LESIONS IN Tg.AC HEMIZYGOUS MICE IN THE DRINKING WATER STUDIES OF SODIUM BROMATE

TABLE B1
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund			1	
Natural deaths	2	2		1
Survivors				
Terminal sacrifice	13	13	14	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Stomach, forestomach	(15)	(15)	(15)	(15)
Squamous cell papilloma	3 (20%)	2 (13%)	8 (53%)	3 (20%)
Squamous cell papilloma, multiple	4 (27%)			
Tooth	(3)	(3)	(4)	(1)
Odontogenic tumor	3 (100%)	3 (100%)	4 (100%)	1 (100%)
Integumentary System				
Skin		(2)	(4)	(3)
Squamous cell papilloma		2 (100%)	3 (75%)	2 (67%)
Subcutaneous tissue, fibrosarcoma				1 (33%)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Alveolar/bronchiolar adenoma				2 (13%)
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Hematopoietic System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
Neoplasm Summary				
Total animals with primary neoplasms[b]	8	6	11	7
Total primary neoplasms	10	7	15	9
Total animals with benign neoplasms	7	4	8	5
Total benign neoplasms	7	4	11	7
Total animals with malignant neoplasms				1
Total malignant neoplasms				1
Total animals with uncertain neoplasms-benign or malignant	3	3	4	1
Total uncertain neoplasms	3	3	4	1

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

TABLE B2
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund			1	
Natural deaths	2	2		1
Survivors				
Terminal sacrifice	13	13	14	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Inflammation, chronic active	9 (60%)	4 (27%)	10 (67%)	7 (47%)
Necrosis				1 (7%)
Hepatocyte, vacuolization cytoplasmic	6 (40%)	4 (27%)	7 (47%)	4 (27%)
Mesentery	(1)		(1)	
Fat, fibrosis	1 (100%)			
Fat, inflammation, chronic			1 (100%)	
Fat, necrosis	1 (100%)			
Stomach, forestomach	(15)	(15)	(15)	(15)
Epithelium, hyperkeratosis	1 (7%)	1 (7%)	2 (13%)	
Epithelium, hyperplasia	1 (7%)	1 (7%)	2 (13%)	2 (13%)
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Hypertrophy	4 (27%)	6 (40%)	6 (40%)	4 (27%)
Subcapsular, hyperplasia	1 (7%)	1 (7%)		1 (7%)
Parathyroid gland	(1)		(2)	
Cyst	1 (100%)		2 (100%)	
Pituitary gland	(15)	(14)	(15)	(15)
Pars distalis, cyst			4 (27%)	
Thyroid gland	(15)	(14)	(15)	(15)
Infiltration cellular, lymphocyte		1 (7%)	1 (7%)	2 (13%)
Follicle, depletion secretory	4 (27%)	6 (43%)	15 (100%)	15 (100%)
Follicular cell, hypertrophy	1 (7%)	2 (14%)	12 (80%)	15 (100%)
Genital System				
Epididymis	(15)	(15)	(15)	(15)
Degeneration			2 (13%)	2 (13%)
Preputial gland	(1)		(1)	
Duct, ectasia	1 (100%)		1 (100%)	
Testes	(15)	(15)	(15)	(15)
Cyst			3 (20%)	
Germinal epithelium, degeneration	1 (7%)		3 (20%)	2 (13%)

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

TABLE B2
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node				(1)
Mediastinal, necrosis, lymphoid				1 (100%)
Lymph node, mandibular	(15)	(15)	(15)	(15)
Hyperplasia, lymphoid	3 (20%)	1 (7%)	3 (20%)	1 (7%)
Necrosis, lymphoid				1 (7%)
Lymph node, mesenteric	(15)	(15)	(15)	(15)
Necrosis, lymphoid				1 (7%)
Spleen	(15)	(15)	(15)	(15)
Atrophy	1 (7%)	1 (7%)		1 (7%)
Hematopoietic cell proliferation	1 (7%)			3 (20%)
Lymphoid follicle, necrosis, lymphoid				1 (7%)
Thymus	(15)	(15)	(14)	(15)
Atrophy	2 (13%)	1 (7%)	1 (7%)	2 (13%)
Cyst	2 (13%)			
Ectopic parathyroid gland				1 (7%)
Thymocyte, necrosis				1 (7%)
Integumentary System				
Skin		(2)	(4)	(3)
Epidermis, hyperkeratosis				1 (33%)
Epidermis, hyperplasia, focal			1 (25%)	2 (67%)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Inflammation, chronic active			1 (7%)	
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Mineralization	1 (7%)			
Nephropathy	1 (7%)	7 (47%)	10 (67%)	14 (93%)
Renal tubule, degeneration				10 (67%)
Renal tubule, dilatation			1 (7%)	
Renal tubule, hypertrophy				2 (13%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

TABLE B3
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	1		
Natural deaths	3	5	5	3
Survivors				
Terminal sacrifice	10	9	10	12
Animals examined microscopically	15	15	15	15
Alimentary System				
Intestine large, rectum	(1)			
Anus, squamous cell papilloma	1 (100%)			
Liver	(15)	(15)	(15)	(15)
Salivary glands	(1)			
Carcinoma	1 (100%)			
Stomach, forestomach	(15)	(15)	(15)	(15)
Squamous cell papilloma	5 (33%)	2 (13%)		3 (20%)
Squamous cell papilloma, multiple	1 (7%)	1 (7%)	2 (13%)	3 (20%)
Tooth	(1)	(3)	(2)	(4)
Odontogenic tumor	1 (100%)	2 (67%)	2 (100%)	4 (100%)
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Adrenal medulla	(15)	(15)	(15)	(15)
Pituitary gland	(15)	(15)	(15)	(15)
Genital System				
Ovary	(15)	(15)	(14)	(15)
Hematopoietic System				
Lymph node	(1)	(1)	(3)	
Lymph node, mandibular	(15)	(15)	(15)	(15)
Lymph node, mesenteric	(15)	(15)	(14)	(14)
Spleen	(15)	(15)	(15)	(15)
Thymus	(15)	(15)	(15)	(15)
Integumentary System				
Skin	(6)	(5)	(2)	(7)
Squamous cell papilloma	5 (83%)	2 (40%)	1 (50%)	4 (57%)
Squamous cell papilloma, multiple	1 (17%)	1 (20%)		1 (14%)
Vulva, squamous cell papilloma		1 (20%)		
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Alveolar/bronchiolar adenoma			1 (7%)	2 (13%)

TABLE B3
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Systemic Lesions				
Multiple organs[b]	(15)	(15)	(15)	(15)
Leukemia erythrocytic	1 (7%)	2 (13%)	3 (20%)	1 (7%)
Lymphoma malignant	1 (7%)	1 (7%)	1 (7%)	
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	10	8	7	10
Total primary neoplasms	17	12	10	18
Total animals with benign neoplasms	9	5	4	9
Total benign neoplasms	13	7	4	13
Total animals with malignant neoplasms	3	3	4	1
Total malignant neoplasms	3	3	4	1
Total animals with uncertain neoplasms-benign or malignant	1	2	2	4
Total uncertain neoplasms	1	2	2	4

[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 B4
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund	2	1		
Natural deaths	3	5	5	3
Survivors				
Terminal sacrifice	10	9	10	12
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation	1 (7%)	1 (7%)		1 (7%)
Inflammation, chronic active	11 (73%)	9 (60%)	10 (67%)	12 (80%)
Necrosis	1 (7%)			1 (7%)
Hepatocyte, vacuolization cytoplasmic	5 (33%)		5 (33%)	5 (33%)
Mesentery	(1)			
Fat, congestion	1 (100%)			
Fat, hemorrhage	1 (100%)			
Stomach, forestomach	(15)	(15)	(15)	(15)
Epithelium, hyperkeratosis	4 (27%)	3 (20%)	3 (20%)	7 (47%)
Epithelium, hyperplasia	5 (33%)	3 (20%)	3 (20%)	8 (53%)
Tooth	(1)	(3)	(2)	(4)
Inflammation, chronic active		1 (33%)		
Cardiovascular System				
Blood vessel	(1)			
Inflammation, chronic	1 (100%)			
Necrosis, fibrinoid	1 (100%)			
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Mineralization		1 (7%)		
Necrosis		1 (7%)		
Subcapsular, hyperplasia	4 (27%)	6 (40%)	2 (13%)	2 (13%)
Pituitary gland	(15)	(15)	(15)	(15)
Pars distalis, cyst	1 (7%)			2 (13%)
Pars distalis, hypertrophy				6 (40%)
Thyroid gland	(15)	(13)	(13)	(15)
Infiltration cellular, lymphocyte			5 (38%)	11 (73%)
Inflammation, chronic active	1 (7%)			
Follicle, depletion secretory	7 (47%)	7 (54%)	11 (85%)	14 (93%)
Follicular cell, hypertrophy	2 (13%)	2 (15%)	11 (85%)	13 (87%)
Genital System				
Ovary	(15)	(15)	(14)	(15)
Cyst	1 (7%)		1 (7%)	
Mineralization			1 (7%)	
Pigmentation, hemosiderin	1 (7%)		1 (7%)	
Uterus	(15)	(15)	(15)	(15)
Endometrium, hyperplasia, cystic	4 (27%)	7 (47%)	6 (40%)	3 (20%)

[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 Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node, mandibular	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation		1 (7%)		
Hyperplasia, lymphoid		4 (27%)	2 (13%)	5 (33%)
Necrosis, lymphoid		1 (7%)		
Lymph node, mesenteric	(15)	(15)	(14)	(14)
Hyperplasia, lymphoid			1 (7%)	
Necrosis, lymphoid			1 (7%)	
Spleen	(15)	(15)	(15)	(15)
Atrophy	1 (7%)	1 (7%)	1 (7%)	2 (13%)
Hematopoietic cell proliferation	2 (13%)	3 (20%)	1 (7%)	4 (27%)
Necrosis				1 (7%)
Thymus	(15)	(15)	(15)	(15)
Atrophy	3 (20%)	3 (20%)	3 (20%)	4 (27%)
Cyst				1 (7%)
Thymocyte, necrosis	2 (13%)			2 (13%)
Integumentary System				
Skin	(6)	(5)	(2)	(7)
Epidermis, hyperkeratosis				2 (29%)
Epidermis, hyperplasia, focal				2 (29%)
Subcutaneous tissue, edema		1 (20%)		
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Hemorrhage			1 (7%)	
Inflammation, chronic active		3 (20%)		1 (7%)
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Mineralization				1 (7%)
Nephropathy	2 (13%)	2 (13%)	10 (67%)	13 (87%)
Artery, inflammation, chronic	2 (13%)			
Renal tubule, degeneration			2 (13%)	8 (53%)
Renal tubule, dilatation	1 (7%)	2 (13%)		1 (7%)
Renal tubule, hypertrophy		1 (7%)	5 (33%)	12 (80%)
Renal tubule, necrosis				1 (7%)

Systems Examined with No Nonneoplastic Lesions Observed
General Body System
Musculoskeletal System
Nervous System
Special Senses System

TABLE B5
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	2	2	4	3
Natural deaths	2	1		3
Survivors				
Terminal sacrifice	6	7	6	4
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Salivary glands		(1)		
Carcinoma		1 (100%)		
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma	2 (20%)	3 (30%)	1 (10%)	1 (10%)
Squamous cell papilloma, multiple	2 (20%)	1 (10%)		
Tooth	(3)	(2)	(4)	(2)
Odontogenic tumor	3 (100%)	2 (100%)	3 (75%)	2 (100%)
Odontogenic tumor, multiple			1 (25%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pituitary gland	(10)	(10)	(10)	(10)
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Hematopoietic System				
Lymph node				(1)
Lymph node, mandibular	(9)	(10)	(10)	(7)
Spleen	(10)	(10)	(10)	(10)
Integumentary System				
Skin	(9)	(9)	(9)	(8)
Squamous cell papilloma		2 (22%)	1 (11%)	3 (38%)
Squamous cell papilloma, multiple	5 (56%)	6 (67%)	5 (56%)	4 (50%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)	3 (30%)	1 (10%)	
Trachea				(1)
Adenoma				1 (100%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)

TABLE B5
Summary of the Incidence of Neoplasms in Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia erythrocytic	2 (20%)		2 (20%)	2 (20%)
Lymphoma malignant		1 (10%)		
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	10	9	10	9
Total primary neoplasms	15	19	14	13
Total animals with benign neoplasms	7	8	7	8
Total benign neoplasms	10	15	8	9
Total animals with malignant neoplasms	2	2	2	2
Total malignant neoplasms	2	2	2	2
Total animals with uncertain neoplasms-benign or malignant	3	2	4	2
Total uncertain neoplasms	3	2	4	2

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

TABLE B6
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	2	2	4	3
Natural deaths	2	1		3
Survivors				
Terminal sacrifice	6	7	6	4
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)		2 (20%)	1 (10%)
Inflammation, chronic active	5 (50%)	5 (50%)	7 (70%)	4 (40%)
Hepatocyte, fatty change	2 (20%)		1 (10%)	
Hepatocyte, necrosis	1 (10%)			
Hepatocyte, vacuolization cytoplasmic	5 (50%)	6 (60%)	6 (60%)	3 (30%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Epithelium, hyperkeratosis	2 (20%)	2 (20%)	1 (10%)	2 (20%)
Epithelium, hyperplasia	4 (40%)	2 (20%)	3 (30%)	5 (50%)
Epithelium, hyperplasia, focal		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hypertrophy	5 (50%)	7 (70%)	6 (60%)	1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, cyst	1 (10%)			
Pars distalis, hypertrophy				2 (20%)
Thyroid gland	(10)	(10)	(10)	(9)
Infiltration cellular, lymphocyte				4 (44%)
Follicle, cyst		1 (10%)		
Follicle, depletion secretory	3 (30%)	4 (40%)	4 (40%)	7 (78%)
Follicular cell, hypertrophy		6 (60%)	8 (80%)	8 (89%)
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Cyst	1 (10%)			
Degeneration	1 (10%)	1 (10%)		7 (70%)
Granuloma sperm			1 (10%)	
Inflammation, chronic active	1 (10%)			
Preputial gland		(2)	(3)	(1)
Atrophy		1 (50%)	1 (33%)	
Duct, ectasia		2 (100%)	2 (67%)	1 (100%)
Testes	(10)	(10)	(10)	(10)
Mineralization		1 (10%)		
Bilateral, germinal epithelium, degeneration			3 (30%)	8 (80%)
Germinal epithelium, degeneration	1 (10%)	1 (10%)	2 (20%)	
Interstitial cell, hyperplasia				3 (30%)

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

TABLE B6
Summary of the Incidence of Nonneoplastic Lesions in Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node, mandibular	(9)	(10)	(10)	(7)
Hyperplasia, lymphoid	2 (22%)		4 (40%)	1 (14%)
Lymph node, mesenteric	(9)	(10)	(10)	(9)
Hyperplasia, lymphoid			1 (10%)	
Spleen	(10)	(10)	(10)	(10)
Atrophy				1 (10%)
Hematopoietic cell proliferation		1 (10%)	2 (20%)	
Thymus	(10)	(10)	(9)	(9)
Atrophy	5 (50%)	1 (10%)	3 (33%)	6 (67%)
Cyst	3 (30%)	1 (10%)		1 (11%)
Integumentary System				
Skin	(9)	(9)	(9)	(8)
Inflammation, chronic active	1 (11%)	1 (11%)		
Epidermis, hyperplasia, focal	3 (33%)	4 (44%)	3 (33%)	1 (13%)
Hair follicle, sebaceous gland, atrophy		1 (11%)		
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Inflammation, chronic active		1 (10%)	1 (10%)	
Thrombosis	1 (10%)			
Alveolar epithelium, hyperplasia				1 (10%)
Alveolus, infiltration cellular, histiocyte	1 (10%)			
Perivascular, infiltration cellular, lymphocyte	1 (10%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Hydronephrosis				2 (20%)
Inflammation			1 (10%)	
Mineralization				1 (10%)
Nephropathy	7 (70%)	6 (60%)	7 (70%)	10 (100%)
Cortex, cyst	1 (10%)			1 (10%)
Glomerulus, inflammation, membranoproliferative	2 (20%)			2 (20%)
Renal tubule, degeneration			1 (10%)	8 (80%)
Renal tubule, hypertrophy			1 (10%)	6 (60%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

TABLE B7
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	3	4	4	7
Natural deaths		1	2	1
Survivors				
Terminal sacrifice	7	5	4	2
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Salivary glands	(1)	(1)	(2)	(2)
Carcinoma	1 (100%)		2 (100%)	2 (100%)
Carcinoma, metastatic, Zymbal's gland		1 (100%)		
Stomach, forestomach	(10)	(10)	(10)	(10)
Squamous cell papilloma		2 (20%)	3 (30%)	
Squamous cell papilloma, multiple	1 (10%)	2 (20%)		1 (10%)
Tooth	(3)	(5)	(2)	(5)
Odontogenic tumor	2 (67%)	4 (80%)	1 (50%)	5 (100%)
Odontogenic tumor, multiple	1 (33%)	1 (20%)	1 (50%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pituitary gland	(10)	(10)	(9)	(10)
Genital System				
Ovary	(10)	(9)	(10)	(10)
Luteoma	1 (10%)		1 (10%)	
Uterus	(10)	(10)	(10)	(10)
Hematopoietic System				
Lymph node	(1)	(2)		
Lymph node, mandibular	(9)	(10)	(10)	(9)
Carcinoma, metastatic, uncertain primary site	1 (11%)			
Carcinoma, metastatic, Zymbal's gland		1 (10%)		
Lymph node, mesenteric	(9)	(9)	(10)	(10)
Spleen	(10)	(10)	(10)	(10)
Thymus	(10)	(10)	(10)	(10)
Integumentary System				
Mammary gland		(1)		
Adenocarcinoma		1 (100%)		
Skin	(6)	(8)	(8)	(4)
Squamous cell papilloma	2 (33%)	3 (38%)	3 (38%)	
Squamous cell papilloma, multiple	3 (50%)	5 (63%)	4 (50%)	1 (25%)
Subcutaneous tissue, fibrosarcoma		1 (13%)		

TABLE B7
Summary of the Incidence of Neoplasms in Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma	1 (10%)	1 (10%)	1 (10%)	
Carcinoma, metastatic, Zymbal's gland		1 (10%)		
Special Senses System				
Zymbal's gland		(1)	(1)	
Carcinoma		1 (100%)		
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia erythrocytic		2 (20%)	2 (20%)	1 (10%)
Lymphoma malignant			1 (10%)	
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	8	9	9	8
Total primary neoplasms	12	23	19	10
Total animals with benign neoplasms	6	8	8	2
Total benign neoplasms	8	13	12	2
Total animals with malignant neoplasms	1	5	5	3
Total malignant neoplasms	1	5	5	3
Total animals with metastatic neoplasms	1	1		
Total metastatic neoplasms	1	3		
Total animals with malignant neoplasms of uncertain primary site	1			
Total animals with uncertain neoplasms-benign or malignant	3	5	2	5
Total uncertain neoplasms	3	5	2	5

[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 B8
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	3	4	4	7
Natural deaths		1	2	1
Survivors				
Terminal sacrifice	7	5	4	2
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	3 (30%)	4 (40%)	6 (60%)	1 (10%)
Inflammation, chronic active	10 (100%)	6 (60%)	7 (70%)	5 (50%)
Mineralization	1 (10%)			
Hepatocyte, fatty change			1 (10%)	
Hepatocyte, necrosis	1 (10%)	1 (10%)		1 (10%)
Hepatocyte, vacuolization cytoplasmic	7 (70%)	4 (40%)	4 (40%)	3 (30%)
Mesentery	(2)			
Fat, fibrosis	1 (50%)			
Fat, necrosis	2 (100%)			
Stomach, forestomach	(10)	(10)	(10)	(10)
Epithelium, hyperkeratosis	1 (10%)	2 (20%)	1 (10%)	7 (70%)
Epithelium, hyperplasia	5 (50%)	6 (60%)	4 (40%)	8 (80%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)		1 (10%)
Mineralization	1 (10%)	2 (20%)		
Subcapsular, hyperplasia	5 (50%)	6 (60%)	1 (10%)	
Parathyroid gland				(1)
Necrosis				1 (100%)
Pituitary gland	(10)	(10)	(9)	(10)
Pars distalis, cyst	3 (30%)	2 (20%)		
Pars distalis, hypertrophy			2 (22%)	6 (60%)
Pars distalis, mineralization				1 (10%)
Thyroid gland	(10)	(9)	(10)	(10)
Infiltration cellular, lymphocyte		2 (22%)	7 (70%)	8 (80%)
Follicle, degeneration		1 (11%)		
Follicle, depletion secretory	1 (10%)	8 (89%)	9 (90%)	10 (100%)
Follicular cell, hypertrophy		8 (89%)	10 (100%)	10 (100%)
Genital System				
Ovary	(10)	(9)	(10)	(10)
Atrophy	1 (10%)		1 (10%)	2 (20%)
Cyst	1 (10%)	1 (11%)		
Inflammation, chronic active	1 (10%)	3 (33%)	1 (10%)	
Uterus	(10)	(10)	(10)	(10)
Inflammation, suppurative		3 (30%)		
Endometrium, hyperplasia, cystic	8 (80%)	7 (70%)	5 (50%)	2 (20%)

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

TABLE B8
Summary of the Incidence of Nonneoplastic Lesions in Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node	(1)	(2)		
Mediastinal, hyperplasia, lymphoid		1 (50%)		
Lymph node, mandibular	(9)	(10)	(10)	(9)
Hyperplasia, lymphoid	2 (22%)	4 (40%)	2 (20%)	2 (22%)
Inflammation, chronic active			1 (10%)	
Lymph node, mesenteric	(9)	(9)	(10)	(10)
Hyperplasia, lymphoid		1 (11%)		
Infiltration cellular, polymorphonuclear		1 (11%)		
Spleen	(10)	(10)	(10)	(10)
Atrophy				1 (10%)
Hematopoietic cell proliferation	3 (30%)	3 (30%)	6 (60%)	4 (40%)
Thymus	(10)	(10)	(10)	(10)
Atrophy	2 (20%)	5 (50%)	6 (60%)	9 (90%)
Cyst			1 (10%)	1 (10%)
Integumentary System				
Skin	(6)	(8)	(8)	(4)
Inflammation, chronic active	1 (17%)	1 (13%)		
Epidermis, hyperplasia, focal	5 (83%)	3 (38%)	2 (25%)	3 (75%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia			1 (10%)	
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization			1 (10%)	2 (20%)
Nephropathy	6 (60%)	6 (60%)	8 (80%)	8 (80%)
Cortex, cyst		2 (20%)		
Glomerulus, inflammation, membranoproliferative		1 (10%)	2 (20%)	1 (10%)
Renal tubule, degeneration				7 (70%)
Renal tubule, hypertrophy			2 (20%)	5 (50%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

APPENDIX C
SUMMARY OF LESIONS IN p53 HAPLOINSUFFICIENT MICE IN THE DRINKING WATER STUDIES OF SODIUM BROMATE

TABLE C1
Summary of the Incidence of Neoplasms in Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund		1	1	
Natural deaths	1			1
Survivors				
Terminal sacrifice	14	14	14	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Intestine large, cecum	(15)	(15)	(15)	(15)
Polyp adenomatous			1 (7%)	
Intestine small, jejunum	(15)	(15)	(15)	(15)
Carcinoma				1 (7%)
Liver	(15)	(15)	(15)	(15)
Mesentery	(1)	(1)		
Salivary glands		(1)		
Endocrine System				
Adrenal cortex	(14)	(15)	(15)	(15)
Adrenal medulla	(14)	(15)	(15)	(15)
Pituitary gland	(15)	(15)	(15)	(15)
Thyroid gland	(15)	(15)	(15)	(15)
Hematopoietic System				
Lymph node	(1)			
Lymph node, mandibular	(15)	(15)	(15)	(15)
Lymph node, mesenteric	(15)	(15)	(15)	(15)
Spleen	(15)	(15)	(15)	(15)
Thymus	(14)	(15)	(15)	(15)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Trachea		(1)		
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Systemic Lesions				
Multiple organs[b]	(15)	(15)	(15)	(15)
Lymphoma malignant	1 (7%)	1 (7%)	1 (7%)	1 (7%)

TABLE C1
Summary of the Incidence of Neoplasms in Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	1	1	2	2
Total primary neoplasms	1	1	2	2
Total animals with benign neoplasms			1	
Total benign neoplasms			1	
Total animals with malignant neoplasms	1	1	1	2
Total malignant neoplasms	1	1	1	2

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

TABLE C2
Summary of the Incidence of Nonneoplastic Lesions in Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Moribund		1	1	
Natural deaths	1			1
Survivors				
Terminal sacrifice	14	14	14	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation		1 (7%)		
Inflammation, chronic active	12 (80%)	12 (80%)	10 (67%)	14 (93%)
Hepatocyte, fatty change	10 (67%)	13 (87%)	10 (67%)	8 (53%)
Hepatocyte, vacuolization cytoplasmic	13 (87%)	14 (93%)	12 (80%)	14 (93%)
Stomach, forestomach	(15)	(15)	(15)	(14)
Epithelium, hyperplasia	3 (20%)	3 (20%)	1 (7%)	3 (21%)
Endocrine System				
Adrenal cortex	(14)	(15)	(15)	(15)
Accessory adrenal cortical nodule		1 (7%)		
Hypertrophy	1 (7%)		2 (13%)	
Subcapsular, hyperplasia	1 (7%)	2 (13%)	2 (13%)	3 (20%)
Pituitary gland	(15)	(15)	(15)	(15)
Pars distalis, cyst	4 (27%)	1 (7%)	3 (20%)	3 (20%)
Pars distalis, hyperplasia	2 (13%)			
Thyroid gland	(15)	(15)	(15)	(15)
Ectopic thymus			1 (7%)	1 (7%)
Infiltration cellular, lymphocyte	1 (7%)	1 (7%)	1 (7%)	
Genital System				
Epididymis	(15)	(15)	(15)	(15)
Degeneration	1 (7%)			
Granuloma sperm			1 (7%)	
Testes	(15)	(15)	(15)	(15)
Cyst	1 (7%)			
Mineralization	1 (7%)			
Germinal epithelium, degeneration	6 (40%)	3 (20%)	3 (20%)	2 (13%)
Hematopoietic System				
Lymph node, mandibular	(15)	(15)	(15)	(15)
Hyperplasia, lymphoid	1 (7%)	2 (13%)	1 (7%)	
Spleen	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation		1 (7%)		1 (7%)
Thymus	(14)	(15)	(15)	(15)
Cyst	7 (50%)	6 (40%)	2 (13%)	2 (13%)
Ectopic parathyroid gland	1 (7%)			
Ectopic thyroid	1 (7%)			
Hyperplasia, lymphoid			1 (7%)	

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

TABLE C2
Summary of the Incidence of Nonneoplastic Lesions in Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Inflammation, chronic active	2 (13%)	1 (7%)		
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Nephropathy	5 (33%)	7 (47%)	3 (20%)	3 (20%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System

TABLE C3
Summary of the Incidence of Neoplasms in Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Natural deaths	1			1
Survivors				
Terminal sacrifice	14	15	15	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Liver	(15)	(15)	(15)	(15)
Hemangiosarcoma, metastatic, mesentery				1 (7%)
Mesentery				(1)
Hemangiosarcoma				1 (100%)
Genital System				
Uterus	(15)	(15)	(15)	(15)
Polyp stromal	1 (7%)	1 (7%)	1 (7%)	
Hematopoietic System				
Lymph node, mandibular	(15)	(15)	(15)	(15)
Lymph node, mesenteric	(14)	(12)	(14)	(14)
Spleen	(15)	(15)	(15)	(15)
Thymus	(15)	(15)	(15)	(15)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Systemic Lesions				
Multiple organs[b]	(15)	(15)	(15)	(15)
Lymphoma malignant	1 (7%)			

TABLE C3
Summary of the Incidence of Neoplasms in Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	2	1	1	1
Total primary neoplasms	2	1	1	1
Total animals with benign neoplasms	1	1	1	
Total benign neoplasms	1	1	1	
Total animals with malignant neoplasms	1			1
Total malignant neoplasms	1			1
Total animals with metastatic neoplasms				1
Total metastatic neoplasms				1

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	15	15	15	15
Early deaths				
Natural deaths	1			1
Survivors				
Terminal sacrifice	14	15	15	14
Animals examined microscopically	15	15	15	15
Alimentary System				
Intestine small, jejunum	(15)	(15)	(15)	(15)
Diverticulum			1 (7%)	
Liver	(15)	(15)	(15)	(15)
Angiectasis				1 (7%)
Hematopoietic cell proliferation				1 (7%)
Inflammation, chronic active	14 (93%)	13 (87%)	14 (93%)	14 (93%)
Hepatocyte, fatty change	1 (7%)			
Hepatocyte, vacuolization cytoplasmic	13 (87%)	14 (93%)	12 (80%)	12 (80%)
Stomach, forestomach	(15)	(15)	(15)	(15)
Inflammation				1 (7%)
Inflammation, chronic active	1 (7%)			
Epithelium, hyperplasia	4 (27%)	1 (7%)	2 (13%)	2 (13%)
Endocrine System				
Adrenal cortex	(15)	(15)	(15)	(15)
Accessory adrenal cortical nodule	1 (7%)			
Subcapsular, hyperplasia	13 (87%)	12 (80%)	13 (87%)	14 (93%)
Parathyroid gland	(1)		(1)	
Cyst	1 (100%)		1 (100%)	
Pituitary gland	(15)	(15)	(15)	(15)
Pars distalis, cyst				1 (7%)
Pars distalis, hyperplasia			1 (7%)	1 (7%)
Thyroid gland	(15)	(15)	(15)	(15)
Ectopic thymus	1 (7%)	2 (13%)	2 (13%)	
Infiltration cellular, lymphocyte		1 (7%)	2 (13%)	
Follicle, depletion secretory				2 (13%)
Follicular cell, hypertrophy				2 (13%)
Genital System				
Ovary	(15)	(15)	(15)	(15)
Cyst	1 (7%)	1 (7%)	2 (13%)	1 (7%)
Uterus	(15)	(15)	(15)	(15)
Inflammation, suppurative	1 (7%)		1 (7%)	
Endometrium, hyperplasia, cystic	11 (73%)	10 (67%)	10 (67%)	10 (67%)

[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 Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node, mandibular	(15)	(15)	(15)	(15)
Hyperplasia, lymphoid		2 (13%)	1 (7%)	1 (7%)
Spleen	(15)	(15)	(15)	(15)
Hematopoietic cell proliferation	1 (7%)		2 (13%)	1 (7%)
Thymus	(15)	(15)	(15)	(15)
Atrophy				1 (7%)
Cyst	4 (27%)	7 (47%)	12 (80%)	3 (20%)
Ectopic parathyroid gland		2 (13%)	1 (7%)	2 (13%)
Ectopic thyroid				2 (13%)
Respiratory System				
Lung	(15)	(15)	(15)	(15)
Inflammation, chronic active	1 (7%)			
Urinary System				
Kidney	(15)	(15)	(15)	(15)
Hydronephrosis				1 (7%)
Nephropathy			2 (13%)	2 (13%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System

TABLE C5
Summary of the Incidence of Neoplasms in Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1	2		
Natural deaths			2	1
Survivors				
Terminal sacrifice	9	8	8	9
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hemangiosarcoma		1 (10%)		
Hepatocellular adenoma			1 (10%)	
Osteosarcoma, metastatic, bone	1 (10%)			
Mesentery	(1)			
Fat, osteosarcoma, metastatic, bone	1 (100%)			
Hematopoietic System				
Thymus	(10)	(10)	(10)	(10)
Integumentary System				
Skin	(1)	(1)		
Subcutaneous tissue, osteosarcoma, metastatic, bone	1 (100%)			
Musculoskeletal System				
Bone	(1)			
Humerus, osteosarcoma	1 (100%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Osteosarcoma, metastatic, bone	1 (10%)			
Urinary System				
Kidney	(10)	(10)	(9)	(10)
Osteosarcoma, metastatic, bone	1 (10%)			
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant		2 (20%)		1 (10%)

TABLE C5
Summary of the Incidence of Neoplasms in Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	1	3	1	1
Total primary neoplasms	1	3	1	1
Total animals with benign neoplasms			1	
Total benign neoplasms			1	
Total animals with malignant neoplasms	1	3		1
Total malignant neoplasms	1	3		1
Total animals with metastatic neoplasms	1			
Total metastatic neoplasms	5			

[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 C6
Summary of the Incidence of Nonneoplastic Lesions in Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund	1	2		
Natural deaths			2	1
Survivors				
Terminal sacrifice	9	8	8	9
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Infiltration cellular, mononuclear cell				1 (10%)
Inflammation, chronic active	9 (90%)	6 (60%)	8 (80%)	9 (90%)
Hepatocyte, fatty change	7 (70%)	9 (90%)	9 (90%)	6 (60%)
Hepatocyte, necrosis	1 (10%)			
Hepatocyte, vacuolization cytoplasmic	9 (90%)	9 (90%)	10 (100%)	10 (100%)
Salivary glands				(1)
Duct, hyperplasia				1 (100%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)	2 (20%)		
Epithelium, hyperkeratosis	1 (10%)	3 (30%)	1 (10%)	
Epithelium, hyperplasia	2 (20%)	4 (40%)		3 (30%)
Epithelium, ulcer	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule			1 (10%)	1 (10%)
Hyperplasia			1 (10%)	
Hypertrophy	1 (10%)	1 (10%)	1 (10%)	3 (30%)
Inflammation, chronic active		1 (10%)		
Subcapsular, hyperplasia	3 (30%)	3 (30%)	2 (20%)	3 (30%)
Pituitary gland	(10)	(9)	(10)	(9)
Pars distalis, cyst	3 (30%)	1 (11%)	3 (30%)	1 (11%)
Pars distalis, hyperplasia			1 (10%)	
Thyroid gland	(10)	(10)	(10)	(9)
Infiltration cellular, lymphocyte	1 (10%)			
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Atrophy	1 (10%)			
Degeneration		2 (20%)		
Infiltration cellular, lymphocyte				2 (20%)
Inflammation, chronic active		2 (20%)		
Testes	(10)	(10)	(10)	(10)
Mineralization		2 (20%)		
Germinal epithelium, degeneration	2 (20%)	4 (40%)	5 (50%)	1 (10%)
Germinal epithelium, necrosis	1 (10%)			

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

TABLE C6
Summary of the Incidence of Nonneoplastic Lesions in Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node	(1)			(1)
Bronchial, hyperplasia	1 (100%)			
Mediastinal, hyperplasia, lymphoid				1 (100%)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)		2 (20%)	1 (10%)
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid			1 (10%)	2 (20%)
Spleen	(10)	(10)	(9)	(10)
Atrophy			1 (11%)	
Hematopoietic cell proliferation	1 (10%)	1 (10%)		
Thymus	(10)	(10)	(10)	(10)
Atrophy	1 (10%)		1 (10%)	1 (10%)
Cyst	5 (50%)	4 (40%)	2 (20%)	7 (70%)
Ectopic parathyroid gland				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Hemorrhage	1 (10%)			
Inflammation, chronic active			1 (10%)	
Urinary System				
Kidney	(10)	(10)	(9)	(10)
Infarct	1 (10%)			
Mineralization			1 (11%)	
Nephropathy	9 (90%)	7 (70%)	7 (78%)	7 (70%)
Cortex, mineralization			1 (11%)	
Papilla, mineralization		1 (10%)		1 (10%)
Pelvis, dilatation				1 (10%)

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System

TABLE C7
Summary of the Incidence of Neoplasms in Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund		1		
Natural deaths	1			
Survivors				
Terminal sacrifice	9	9	10	10
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Pancreas		(1)		
Acinus, carcinoma		1 (100%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Adrenal medulla	(10)	(10)	(10)	(10)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma		1 (10%)		
Thyroid gland	(10)	(10)	(10)	(10)
Follicular cell, adenoma		1 (10%)		
Genital System				
Ovary	(10)	(10)	(10)	(10)
Cystadenoma	1 (10%)			
Hematopoietic System				
Lymph node	(1)		(1)	
Lymph node, mandibular	(10)	(10)	(10)	(10)
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Spleen	(10)	(10)	(10)	(10)
Thymus	(10)	(10)	(10)	(10)
Integumentary System				
Skin		(1)	(1)	(1)
Squamous cell carcinoma			1 (100%)	
Subcutaneous tissue, lipoma				1 (100%)
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Urinary System				
Kidney	(10)	(10)	(10)	(10)

TABLE C7
Summary of the Incidence of Neoplasms in Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Lymphoma malignant	2 (20%)		1 (10%)	
Systems Examined with No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Neoplasm Summary				
Total animals with primary neoplasms[c]	3	3	2	1
Total primary neoplasms	3	3	2	1
Total animals with benign neoplasms	1	2		1
Total benign neoplasms	1	2		1
Total animals with malignant neoplasms	2	1	2	
Total malignant neoplasms	2	1	2	

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

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Disposition Summary				
Animals initially in study	10	10	10	10
Early deaths				
Moribund		1		
Natural deaths	1			
Survivors				
Terminal sacrifice	9	9	10	10
Animals examined microscopically	10	10	10	10
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Angiectasis				2 (20%)
Hematopoietic cell proliferation		1 (10%)		
Inflammation, chronic active	9 (90%)	10 (100%)	8 (80%)	10 (100%)
Mixed cell focus				1 (10%)
Hepatocyte, fatty change	1 (10%)	1 (10%)		
Hepatocyte, vacuolization cytoplasmic	9 (90%)	10 (100%)	8 (80%)	10 (100%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Inflammation, chronic active	1 (10%)			
Epithelium, hyperkeratosis	2 (20%)	1 (10%)		1 (10%)
Epithelium, hyperplasia	2 (20%)	1 (10%)		3 (30%)
Epithelium, ulcer	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	1 (10%)		
Infiltration cellular, lymphocyte	1 (10%)			1 (10%)
Subcapsular, hyperplasia	8 (80%)	9 (90%)	10 (100%)	10 (100%)
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, cyst			2 (20%)	1 (10%)
Pars distalis, hyperplasia		1 (10%)	2 (20%)	
Thyroid gland	(10)	(10)	(10)	(10)
Ectopic thymus	1 (10%)			
Infiltration cellular, lymphocyte	2 (20%)		1 (10%)	1 (10%)
Follicle, cyst				2 (20%)
Genital System				
Ovary	(10)	(10)	(10)	(10)
Atrophy			1 (10%)	
Cyst	3 (30%)	2 (20%)	1 (10%)	2 (20%)
Bilateral, cyst		1 (10%)		
Uterus	(10)	(10)	(10)	(10)
Inflammation, suppurative	1 (10%)			
Endometrium, hyperplasia, cystic	9 (90%)	10 (100%)	8 (80%)	8 (80%)

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

TABLE C8
Summary of the Incidence of Nonneoplastic Lesions in Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Hematopoietic System				
Lymph node, mandibular	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid			1 (10%)	
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation		1 (10%)	1 (10%)	
Hyperplasia, lymphoid			1 (10%)	
Thymus	(10)	(10)	(10)	(10)
Cyst	2 (20%)	4 (40%)	5 (50%)	3 (30%)
Ectopic parathyroid gland			1 (10%)	1 (10%)
Ectopic thyroid				1 (10%)
Integumentary System				
Skin		(1)	(1)	(1)
Hyperkeratosis			1 (100%)	
Hyperplasia			1 (100%)	
Inflammation, chronic active		1 (100%)	1 (100%)	
Ulcer			1 (100%)	
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Alveolar epithelium, hyperplasia				1 (11%)
Perivascular, infiltration cellular, lymphocyte	4 (40%)	3 (30%)	4 (40%)	2 (22%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Mineralization		1 (10%)		1 (10%)
Nephropathy	7 (70%)	7 (70%)	6 (60%)	8 (80%)
Papilla, mineralization		1 (10%)		

Systems Examined with No Nonneoplastic Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Special Senses System

APPENDIX D
GENETIC TOXICOLOGY

TABLE D1
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Tg.AC Hemizygous Mice Following Dermal Administration of Sodium Bromate for 26 Weeks[a]

	Concentration (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Ethanol/water[d]		12	0.92 ± 0.16		3.000 ± 0.25
Sodium bromate	64	11	2.14 ± 0.20	0.0004	3.727 ± 0.24
	128	13	4.42 ± 0.39	0.0000	4.692 ± 0.26
	256	15	5.20 ± 0.42	0.0000	5.000 ± 0.43
			P=0.000[e]		P<0.001[f]
Female					
Ethanol/water		10	1.45 ± 0.31		3.900 ± 0.23
Sodium bromate	64	10	2.60 ± 0.31	0.0053	4.200 ± 0.29
	128	11	3.00 ± 0.44	0.0004	4.818 ± 0.42
	256	11	4.09 ± 0.46	0.0000	5.000 ± 0.43
			P=0.000		P=0.126

[a] Study was performed at SITEK Research Laboratories, Inc. The detailed protocol is presented by MacGregor *et al*. (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the vehicle control, significant at P≤0.008 (ILS, 1990)
[e] Vehicle control (40% USP-grade 95% ethanol/60% water)
[f] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)
Significance of percent PCEs tested by ANOVA using individual animal data

TABLE D2
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Tg.AC Hemizygous Mice Following Administration of Sodium Bromate in Drinking Water for 27 Weeks[a]

	Concentration (mg/L)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Tap water[d]		13	1.42 ± 0.18		3.231 ± 0.17
Sodium bromate	80	13	1.58 ± 0.26	0.3252	3.538 ± 0.24
	400	14	1.96 ± 0.26	0.0638	3.929 ± 0.22
	800	14	5.25 ± 0.73	0.0000	5.357 ± 0.45
			P=0.000[e]		P<0.001[f]
Female					
Tap water		10	1.25 ± 0.40		3.800 ± 0.20
Sodium bromate	80	9	1.61 ± 0.23	0.1754	4.444 ± 0.24
	400	10	3.30 ± 0.35	0.0000	5.200 ± 0.44
	800	12	7.75 ± 1.35	0.0000	7.833 ± 0.67
			P=0.000		P<0.001

[a] Study was performed at SITEK Research Laboratories, Inc. The detailed protocol is presented by MacGregor *et al*. (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the untreated control, significant at P≤0.008 (ILS, 1990)
[e] Untreated control
[f] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)
Significance of percent PCEs tested by ANOVA using individual animal data

TABLE D3
Frequency of Micronuclei in Peripheral Blood Erythrocytes of p53 Haploinsufficient Mice Following Administration of Sodium Bromate in Drinking Water for 27 Weeks[a]

	Concentration (mg/L)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Tap water[d]		14	1.54 ± 0.24		3.357 ± 0.20
Sodium bromate	80	14	1.79 ± 0.31	0.2338	3.143 ± 0.21
	400	14	2.29 ± 0.41	0.0211	3.571 ± 0.42
	800	14	3.86 ± 0.25	0.0000	4.000 ± 0.36
			P=0.000[e]		P=0.246[f]
Female					
Tap water		14	1.18 ± 0.18		3.071 ± 0.16
Sodium bromate	80	15	1.47 ± 0.23	0.1705	3.133 ± 0.22
	400	15	1.97 ± 0.22	0.0086	3.400 ± 0.13
	800	14	3.57 ± 0.25	0.0000	3.357 ± 0.17
			P=0.000		P=0.628

[a] Study was performed at SITEK Research Laboratories, Inc. The detailed protocol is presented by MacGregor *et al*. (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the untreated control, significant at P≤0.008 (ILS, 1990)
[e] Untreated control
[f] Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)
Significance of percent PCEs tested by ANOVA using individual animal data

APPENDIX E
CLINICAL PATHOLOGY RESULTS

TABLE E1
Hematology Data for Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
n	12	10	13	12
Hematocrit (%)	42.9 ± 0.5	41.4 ± 0.7	41.9 ± 0.7	41.0 ± 0.6
Hemoglobin (g/dL)	13.9 ± 0.2	13.2 ± 0.2	13.4 ± 0.2	13.0 ± 0.2**
Erythrocytes (10^6/μL)	9.91 ± 0.15	9.47 ± 0.17	9.65 ± 0.18	9.29 ± 0.18*
Reticulocytes (10^6/μL)	0.15 ± 0.02	0.19 ± 0.02	0.19 ± 0.01	0.22 ± 0.02*
Mean cell volume (fL)	43.3 ± 0.4	43.8 ± 0.2	43.4 ± 0.3	44.2 ± 0.3
Mean cell hemoglobin (pg)	14.0 ± 0.2	14.0 ± 0.1	13.9 ± 0.1	14.0 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.3 ± 0.1	32.0 ± 0.1	32.1 ± 0.2	31.7 ± 0.3*
Platelets (10^3/μL)	1,038.2 ± 36.8	997.5 ± 26.1	1,117.9 ± 32.2	1,245.3 ± 70.5*
Leukocytes (10^3/μL)	3.31 ± 0.49	2.90 ± 0.41	3.91 ± 0.50	3.00 ± 0.37
Segmented neutrophils (10^3/μL)	1.08 ± 0.27	0.45 ± 0.07	0.98 ± 0.25	0.70 ± 0.17
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	2.13 ± 0.24	2.36 ± 0.34	2.76 ± 0.30	2.18 ± 0.3
Monocytes (10^3/μL)	0.05 ± 0.02	0.06 ± 0.02	0.15 ± 0.04	0.10 ± 0.03
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.05 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Female				
n	10	10	11	11
Hematocrit (%)	43.4 ± 0.5	42.6 ± 0.5	41.0 ± 0.8*	41.1 ± 0.5**
Hemoglobin (g/dL)	14.3 ± 0.1	13.8 ± 0.2	13.1 ± 0.3**	13.1 ± 0.1**
Erythrocytes (10^6/μL)	9.84 ± 0.19	9.55 ± 0.13	9.45 ± 0.31	9.67 ± 0.25
Reticulocytes (10^6/μL)	0.15 ± 0.01	0.19 ± 0.01	0.21 ± 0.02*	0.21 ± 0.02*
Mean cell volume (fL)	44.1 ± 0.5	44.6 ± 0.2	43.6 ± 0.6	42.7 ± 0.7
Mean cell hemoglobin (pg)	14.5 ± 0.2	14.5 ± 0.1	14.0 ± 0.2*	13.6 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.1	32.5 ± 0.1**	32.0 ± 0.1**	31.8 ± 0.2**
Platelets (10^3/μL)	890.7 ± 38.8	918.3 ± 59.0	924.1 ± 54.9	1,024.6 ± 21.2
Leukocytes (10^3/μL)	5.26 ± 0.58	5.78 ± 0.47	5.01 ± 0.42	5.43 ± 0.27
Segmented neutrophils (10^3/μL)	1.39 ± 0.28	1.01 ± 0.10	1.19 ± 0.30	1.27 ± 0.18
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	3.68 ± 0.31	4.60 ± 0.38	3.62 ± 0.34	3.96 ± 0.23
Monocytes (10^3/μL)	0.12 ± 0.03	0.14 ± 0.04	0.14 ± 0.03	0.15 ± 0.02
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.07 ± 0.03	0.03 ± 0.02	0.06 ± 0.02	0.05 ± 0.02

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

TABLE E2
Hematology Data for Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	12	13	13	14
Hematocrit (%)	40.8 ± 0.5	41.0 ± 0.4	40.1 ± 0.4	41.7 ± 0.4
Hemoglobin (g/dL)	13.3 ± 0.2	13.2 ± 0.1	12.8 ± 0.2*	13.0 ± 0.2
Erythrocytes (10^6/μL)	9.31 ± 0.15	9.40 ± 0.13	9.13 ± 0.12	9.56 ± 0.08
Reticulocytes (10^6/μL)	0.14 ± 0.01	0.15 ± 0.01	0.19 ± 0.01**	0.24 ± 0.02**
Mean cell volume (fL)	43.9 ± 0.2	43.6 ± 0.3	44.0 ± 0.3	43.7 ± 0.3
Mean cell hemoglobin (pg)	14.3 ± 0.1	14.1 ± 0.1	14.0 ± 0.1*	13.6 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.3 ± 0.0*	31.9 ± 0.1**	31.1 ± 0.2**
Platelets (10^3/μL)	1,272.7 ± 47.3	1,229.4 ± 30.9	1,248.5 ± 22.5	1,269.4 ± 22.8
Leukocytes (10^3/μL)	5.25 ± 0.24	4.32 ± 0.34	4.51 ± 0.55	4.96 ± 0.46
Segmented neutrophils (10^3/μL)	1.12 ± 0.17	0.75 ± 0.08	1.13 ± 0.44	1.14 ± 0.45
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	4.08 ± 0.24	3.52 ± 0.27	3.32 ± 0.19	3.74 ± 0.22
Monocytes (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.04 ± 0.02	0.06 ± 0.06
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.04 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Female				
n	10	9	9	12
Hematocrit (%)	44.4 ± 0.7	44.5 ± 0.7	42.4 ± 0.8	41.4 ± 0.6**
Hemoglobin (g/dL)	14.4 ± 0.2	14.5 ± 0.3	13.6 ± 0.3	13.0 ± 0.2
Erythrocytes (10^6/μL)	10.11 ± 0.18	9.96 ± 0.20	9.50 ± 0.29*	9.12 ± 0.21**
Reticulocytes (10^6/μL)	0.14 ± 0.01	0.15 ± 0.02	0.17 ± 0.02	0.33 ± 0.04*
Mean cell volume (fL)	44.0 ± 0.5	44.7 ± 0.5	44.8 ± 0.6	45.5 ± 0.5
Mean cell hemoglobin (pg)	14.3 ± 0.2	14.6 ± 0.2	14.4 ± 0.2	14.2 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.4 ± 0.2	32.6 ± 0.1	32.0 ± 0.1	31.3 ± 0.1**
Platelets (10^3/μL)	877.7 ± 26.8	933.2 ± 68.9	977.6 ± 44.3	1,110.3 ± 59.1**
Leukocytes (10^3/μL)	6.08 ± 0.68	5.52 ± 0.34	5.16 ± 0.35	6.63 ± 0.39
Segmented neutrophils (10^3/μL)	1.38 ± 0.51	1.01 ± 0.26	0.8 ± 0.12	1.47 ± 0.33
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	4.58 ± 0.48	4.42 ± 0.32	4.35 ± 0.29	5.04 ± 0.30
Monocytes (10^3/μL)	0.04 ± 0.02	0.05 ± 0.02	0.01 ± 0.01	0.09 ± 0.03
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.08 ± 0.03	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.01

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

TABLE E3
Hematology Data for p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	14	14	13	14
Hematocrit (%)	46.7 ± 0.4	47.5 ± 0.2	46.4 ± 0.6	47.5 ± 0.7
Hemoglobin (g/dL)	15.2 ± 0.1	15.4 ± 0.1	14.9 ± 0.2	15.2 ± 0.2
Erythrocytes (10^6/μL)	10.41 ± 0.13	10.52 ± 0.08	10.33 ± 0.12	10.87 ± 0.19*
Reticulocytes (10^6/μL)	0.15 ± 0.01	0.16 ± 0.01	0.17 ± 0.02	0.20 ± 0.01*
Mean cell volume (fL)	44.9 ± 0.3	45.2 ± 0.2	44.9 ± 0.2	43.8 ± 0.3
Mean cell hemoglobin (pg)	14.6 ± 0.1	14.6 ± 0.1	14.4 ± 0.1	14.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.5 ± 0.1	32.5 ± 0.1	32.1 ± 0.1	32.0 ± 0.1**
Platelets (10^3/μL)	986.0 ± 16.5	962.0 ± 19.6	974.9 ± 43.0	966.4 ± 31.8
Leukocytes (10^3/μL)	7.79 ± 0.39	7.07 ± 0.25	7.18 ± 0.37	7.60 ± 0.40
Segmented neutrophils (10^3/μL)	1.04 ± 0.15	0.88 ± 0.07	0.92 ± 0.06	0.88 ± 0.09
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	6.67 ± 0.30	6.12 ± 0.27	6.15 ± 0.40	6.62 ± 0.35
Monocytes (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.06 ± 0.02	0.07 ± 0.01	0.07 ± 0.01	0.06 ± 0.01
Female				
n	14	15	15	14
Hematocrit (%)	46.1 ± 0.4	47.2 ± 0.4	48.0 ± 0.6*	47.0 ± 0.4
Hemoglobin (g/dL)	14.8 ± 0.1	15.2 ± 0.1	15.3 ± 0.2*	15.0 ± 0.2
Erythrocytes (10^6/μL)	10.25 ± 0.09	10.49 ± 0.08	10.76 ± 0.13**	10.72 ± 0.09**
Reticulocytes (10^6/μL)	0.20 ± 0.01	0.18 ± 0.01	0.17 ± 0.01	0.20 ± 0.01
Mean cell volume (fL)	45.0 ± 0.2	44.9 ± 0.1	44.7 ± 0.2	43.9 ± 0.2**
Mean cell hemoglobin (pg)	14.4 ± 0.1	14.5 ± 0.1	14.3 ± 0.0	14.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.1	32.3 ± 0.1	32.0 ± 0.1	31.8 ± 0.1
Platelets (10^3/μL)	908.6 ± 17.9	883.1 ± 24.8	901.8 ± 55.4	948.6 ± 57.6
Leukocytes (10^3/μL)	4.07 ± 0.28	4.41 ± 0.34	4.04 ± 0.26	4.06 ± 0.32
Segmented neutrophils (10^3/μL)	0.36 ± 0.03	0.45 ± 0.06	0.35 ± 0.03	0.32 ± 0.04
Bands (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Lymphocytes (10^3/μL)	3.68 ± 0.28	3.92 ± 0.30	3.64 ± 0.25	3.72 ± 0.3
Monocytes (10^3/μL)	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.0
Basophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.02 ± 0.01

* Significantly different ($P \le 0.05$) from the vehicle control group by Dunn's or Shirley's test
** $P \le 0.01$
Statistical tests were performed on unrounded data.

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

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Tg.AC Hemizygous Mice in the 26-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
n	12	11	13	14
Necropsy body wt	35.0 ± 1.9	35.8 ± 1.1	34.4 ± 1.1	32.1 ± 0.6
Heart				
Absolute	0.180 ± 0.007	0.171 ± 0.003	0.178 ± 0.004	0.168 ± 0.006
Relative	5.198 ± 0.109	4.829 ± 0.129	5.240 ± 0.187	5.272 ± 0.132
R. Kidney				
Absolute	0.314 ± 0.011	0.337 ± 0.010	0.333 ± 0.010	0.352 ± 0.013
Relative	9.104 ± 0.315	9.532 ± 0.410	9.770 ± 0.344	11.006 ± 0.305**
Liver				
Absolute	1.656 ± 0.093	1.663 ± 0.043	1.669 ± 0.051	1.702 ± 0.048
Relative	47.362 ± 1.041	46.675 ± 0.877	48.668 ± 0.958	53.359 ± 0.954**
Lung				
Absolute	0.271 ± 0.015	0.302 ± 0.013	0.270 ± 0.017	0.251 ± 0.010
Relative	7.924 ± 0.504	8.468 ± 0.312	7.918 ± 0.505	7.900 ± 0.359
R. Testis				
Absolute	0.088 ± 0.002	0.086 ± 0.002	0.081 ± 0.003	0.082 ± 0.002
Relative	2.571 ± 0.112	2.409 ± 0.075	2.380 ± 0.102	2.600 ± 0.086
Thymus				
Absolute	0.031 ± 0.002	0.036 ± 0.004	0.029 ± 0.003	0.024 ± 0.002
Relative	0.882 ± 0.035	0.998 ± 0.084	0.852 ± 0.061	0.768 ± 0.062
Female				
n	11	10	11	11
Necropsy body wt	28.5 ± 1.6	28.6 ± 1.4	27.8 ± 0.8	28.5 ± 1.1
Heart				
Absolute	0.151 ± 0.005	0.143 ± 0.005	0.136 ± 0.003*	0.137 ± 0.004
Relative	5.378 ± 0.175	5.046 ± 0.119	4.906 ± 0.133	4.857 ± 0.205
R. Kidney				
Absolute	0.211 ± 0.008	0.214 ± 0.008	0.207 ± 0.005	0.214 ± 0.006
Relative	7.487 ± 0.141	7.527 ± 0.222	7.461 ± 0.191	7.556 ± 0.179
Liver				
Absolute	1.468 ± 0.082	1.447 ± 0.067	1.441 ± 0.039	1.445 ± 0.039
Relative	51.575 ± 0.821	50.654 ± 0.670	51.897 ± 1.098	50.989 ± 1.135
Lung				
Absolute	0.259 ± 0.013	0.266 ± 0.014	0.271 ± 0.015	0.231 ± 0.004
Relative	9.202 ± 0.405	9.321 ± 0.327	9.860 ± 0.682	8.196 ± 0.245
Thymus				
Absolute	0.035 ± 0.003	0.037 ± 0.003	0.029 ± 0.002	0.035 ± 0.002
Relative	1.219 ± 0.054	1.292 ± 0.081	1.043 ± 0.070	1.210 ± 0.066

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

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Tg.AC Hemizygous Mice in the 39-Week Dermal Study of Sodium Bromate[a]

	Vehicle Control	64 mg/kg	128 mg/kg	256 mg/kg
Male				
n	8	8	8	8
Necropsy body wt	35.7 ± 2.0	35.3 ± 1.2	34.7 ± 1.1	32.3 ± 1.8
Heart				
Absolute	0.203 ± 0.009	0.191 ± 0.005	0.190 ± 0.006	0.176 ± 0.005**
Relative	5.718 ± 0.196	5.452 ± 0.188	5.479 ± 0.182	5.528 ± 0.210
R. Kidney				
Absolute	0.346 ± 0.019	0.376 ± 0.010	0.391 ± 0.014	0.361 ± 0.022
Relative	9.727 ± 0.364	10.697 ± 0.284*	11.264 ± 0.200**	11.176 ± 0.288**
Liver				
Absolute	1.871 ± 0.128	1.968 ± 0.062	2.040 ± 0.046	1.673 ± 0.106
Relative	52.270 ± 1.637	55.959 ± 1.778	58.986 ± 1.307*	51.791 ± 1.794
Lung				
Absolute	0.246 ± 0.014	0.235 ± 0.011	0.259 ± 0.018	0.243 ± 0.015
Relative	7.078 ± 0.623	6.687 ± 0.352	7.504 ± 0.551	7.590 ± 0.405
R. Testis				
Absolute	0.086 ± 0.004	0.079 ± 0.004	0.084 ± 0.007	0.065 ± 0.006*
Relative	2.430 ± 0.144	2.281 ± 0.175	2.435 ± 0.210	2.020 ± 0.167
Thymus				
Absolute	0.024 ± 0.004	0.026 ± 0.003	0.022 ± 0.003	0.025 ± 0.002
Relative	0.646 ± 0.086	0.737 ± 0.069	0.645 ± 0.099	0.766 ± 0.055
Female				
n	7	7	8	8
Necropsy body wt	33.2 ± 2.2	28.5 ± 0.9	28.5 ± 2.0	29.4 ± 1.1
Heart				
Absolute	0.158 ± 0.008	0.153 ± 0.009	0.142 ± 0.006	0.147 ± 0.005
Relative	4.800 ± 0.209	5.372 ± 0.244	5.056 ± 0.168	5.036 ± 0.197
R. Kidney				
Absolute	0.260 ± 0.008	0.233 ± 0.009	0.233 ± 0.009	0.231 ± 0.006*
Relative	7.944 ± 0.423	8.177 ± 0.186	8.340 ± 0.330	7.862 ± 0.134
Liver				
Absolute	1.725 ± 0.095	1.551 ± 0.065	1.611 ± 0.118	1.692 ± 0.094
Relative	52.362 ± 2.232	54.449 ± 1.879	56.697 ± 2.239	57.274 ± 1.488
Lung				
Absolute	0.223 ± 0.013	0.252 ± 0.019	0.221 ± 0.011	0.230 ± 0.010
Relative	6.747 ± 0.276	8.911 ± 0.770*	8.003 ± 0.657	7.907 ± 0.504
Thymus				
Absolute	0.028 ± 0.003	0.031 ± 0.003	0.028 ± 0.004	0.029 ± 0.003
Relative	0.843 ± 0.065	1.091 ± 0.077	0.972 ± 0.140	0.970 ± 0.058

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

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	13	13	14	14
Necropsy body wt	37.7 ± 1.5	38.9 ± 0.8	34.8 ± 1.5	32.4 ± 0.8**
Heart				
Absolute	0.180 ± 0.005	0.180 ± 0.003	0.168 ± 0.005	0.157 ± 0.004**
Relative	4.825 ± 0.118	4.638 ± 0.069	4.879 ± 0.148	4.875 ± 0.118
R. Kidney				
Absolute	0.317 ± 0.009	0.341 ± 0.007	0.333 ± 0.015	0.323 ± 0.008
Relative	8.482 ± 0.194	8.779 ± 0.166	9.559 ± 0.140**	9.998 ± 0.209**
Liver				
Absolute	1.812 ± 0.067	1.887 ± 0.045	1.794 ± 0.090	1.711 ± 0.029
Relative	48.186 ± 0.749	48.455 ± 0.432	51.393 ± 1.015*	53.061 ± 0.990**
Lung				
Absolute	0.228 ± 0.008	0.230 ± 0.011	0.243 ± 0.008	0.234 ± 0.006
Relative	6.125 ± 0.246	5.936 ± 0.306	7.177 ± 0.432*	7.306 ± 0.272*
R. Testis				
Absolute	0.085 ± 0.002	0.088 ± 0.002	0.086 ± 0.003	0.079 ± 0.003
Relative	2.307 ± 0.094	2.274 ± 0.050	2.548 ± 0.140	2.464 ± 0.116
Thymus				
Absolute	0.042 ± 0.004	0.048 ± 0.004	0.035 ± 0.003	0.034 ± 0.004
Relative	1.101 ± 0.081	1.205 ± 0.091	0.982 ± 0.082	1.028 ± 0.090
Female				
n	10	9	10	12
Necropsy body wt	32.4 ± 1.8	31.3 ± 1.5	33.1 ± 1.4	27.0 ± 1.1*
Heart				
Absolute	0.160 ± 0.007	0.151 ± 0.005	0.150 ± 0.004	0.119 ± 0.006**
Relative	5.012 ± 0.251	4.876 ± 0.123	4.590 ± 0.203	4.389 ± 0.182
R. Kidney				
Absolute	0.226 ± 0.005	0.221 ± 0.007	0.215 ± 0.006	0.203 ± 0.008*
Relative	7.090 ± 0.318	7.179 ± 0.343	6.597 ± 0.289	7.560 ± 0.276
Liver				
Absolute	1.672 ± 0.038	1.574 ± 0.035	1.641 ± 0.053	1.638 ± 0.067
Relative	52.309 ± 1.678	50.952 ± 1.738	50.135 ± 1.911	61.646 ± 3.457*
Lung				
Absolute	0.296 ± 0.009	0.308 ± 0.018	0.277 ± 0.014	0.263 ± 0.010
Relative	9.307 ± 0.452	9.890 ± 0.405	8.595 ± 0.690	9.775 ± 0.252
Thymus				
Absolute	0.042 ± 0.004	0.040 ± 0.006	0.040 ± 0.003	0.032 ± 0.002
Relative	1.303 ± 0.142	1.245 ± 0.139	1.209 ± 0.068	1.175 ± 0.065

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	6	7	6	4
Necropsy body wt	41.7 ± 2.3	41.7 ± 1.2	40.9 ± 2.2	28.4 ± 0.5**
Heart				
Absolute	0.200 ± 0.012	0.191 ± 0.006	0.193 ± 0.009	0.139 ± 0.012**
Relative	4.822 ± 0.212	4.583 ± 0.088	4.738 ± 0.219	4.882 ± 0.355
R. Kidney				
Absolute	0.346 ± 0.014	0.366 ± 0.012	0.351 ± 0.016	0.267 ± 0.007**
Relative	8.399 ± 0.507	8.814 ± 0.326	8.622 ± 0.250	9.406 ± 0.279
Liver				
Absolute	2.093 ± 0.127	2.127 ± 0.071	2.168 ± 0.119	1.751 ± 0.098
Relative	50.149 ± 0.575	50.997 ± 0.699	53.035 ± 0.952	61.739 ± 3.539**
Lung				
Absolute	0.316 ± 0.029	0.246 ± 0.012*	0.254 ± 0.015	0.230 ± 0.015*
Relative	7.651 ± 0.643	5.922 ± 0.296*	6.287 ± 0.483	8.079 ± 0.448
R. Testis				
Absolute	0.092 ± 0.003	0.091 ± 0.003	0.081 ± 0.006	0.053 ± 0.007**
Relative	2.271 ± 0.205	2.194 ± 0.078	1.993 ± 0.164	1.869 ± 0.243
Thymus				
Absolute	0.035 ± 0.008	0.040 ± 0.002	0.033 ± 0.005	0.020 ± 0.002
Relative	0.812 ± 0.165	0.961 ± 0.060	0.795 ± 0.106	0.696 ± 0.070
Female				
n	7	5	4	2
Necropsy body wt	32.8 ± 2.6	31.2 ± 1.3	34.9 ± 2.4	22.6 ± 0.1
Heart				
Absolute	0.177 ± 0.014	0.145 ± 0.012	0.172 ± 0.011	0.096 ± 0.003*
Relative	5.484 ± 0.425	4.635 ± 0.285	4.930 ± 0.059	4.235 ± 0.120
R. Kidney				
Absolute	0.243 ± 0.010	0.246 ± 0.010	0.248 ± 0.011	0.171 ± 0.006**
Relative	7.562 ± 0.364	7.933 ± 0.411	7.151 ± 0.312	7.583 ± 0.249
Liver				
Absolute	1.787 ± 0.100	2.635 ± 0.875	1.996 ± 0.193	1.597 ± 0.036
Relative	55.168 ± 2.344	83.674 ± 26.769	57.328 ± 4.792	70.795 ± 1.417
Lung				
Absolute	0.285 ± 0.030	0.247 ± 0.029	0.242 ± 0.005	0.193 ± 0.019
Relative	8.864 ± 1.055	7.907 ± 0.886	7.022 ± 0.436	8.538 ± 0.839
Thymus				
Absolute	0.031 ± 0.003	0.030 ± 0.006	0.026 ± 0.004	0.022 ± 0.007
Relative	0.945 ± 0.037	0.933 ± 0.174	0.736 ± 0.128	0.953 ± 0.286

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

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	14	14	14	14
Necropsy body wt	47.7 ± 1.5	49.0 ± 0.9	47.8 ± 1.1	46.8 ± 1.1
Heart				
Absolute	0.206 ± 0.009	0.225 ± 0.007	0.213 ± 0.006	0.219 ± 0.007
Relative	4.319 ± 0.124	4.593 ± 0.133	4.469 ± 0.111	4.694 ± 0.168
R. Kidney				
Absolute	0.279 ± 0.011	0.290 ± 0.011	0.291 ± 0.008	0.286 ± 0.010
Relative	5.891 ± 0.250	5.906 ± 0.149	6.104 ± 0.166	6.092 ± 0.151
Liver				
Absolute	2.874 ± 0.212	3.022 ± 0.152	2.724 ± 0.154	2.555 ± 0.161
Relative	59.352 ± 3.046	61.257 ± 2.287	56.591 ± 2.149	53.972 ± 2.262
Lung				
Absolute	0.268 ± 0.016	0.268 ± 0.012	0.277 ± 0.015	0.289 ± 0.018
Relative	5.705 ± 0.404	5.489 ± 0.239	5.817 ± 0.309	6.246 ± 0.449
R. Testis				
Absolute	0.109 ± 0.003	0.111 ± 0.002	0.110 ± 0.002	0.111 ± 0.002
Relative	2.317 ± 0.074	2.279 ± 0.038	2.303 ± 0.044	2.374 ± 0.061
Thymus				
Absolute	0.064 ± 0.004	0.065 ± 0.004	0.072 ± 0.004	0.064 ± 0.003
Relative	1.340 ± 0.056	1.317 ± 0.069	1.527 ± 0.088	1.374 ± 0.060
Female				
n	14	15	15	14
Necropsy body wt	36.0 ± 2.1	35.8 ± 1.7	33.7 ± 2.2	31.6 ± 1.4
Heart				
Absolute	0.160 ± 0.005	0.161 ± 0.004	0.161 ± 0.005	0.156 ± 0.004
Relative	4.580 ± 0.225	4.591 ± 0.157	4.991 ± 0.296	4.999 ± 0.179
R. Kidney				
Absolute	0.194 ± 0.004	0.196 ± 0.006	0.204 ± 0.006	0.198 ± 0.005
Relative	5.592 ± 0.309	5.563 ± 0.146	6.265 ± 0.269	6.348 ± 0.245
Liver				
Absolute	1.640 ± 0.074	1.594 ± 0.048	1.500 ± 0.068	1.498 ± 0.052
Relative	46.062 ± 1.210	45.106 ± 1.012	45.241 ± 1.016	47.663 ± 0.903
Lung				
Absolute	0.270 ± 0.016	0.272 ± 0.016	0.271 ± 0.013	0.284 ± 0.012
Relative	7.741 ± 0.567	7.848 ± 0.589	8.220 ± 0.332	9.118 ± 0.454
Thymus				
Absolute	0.056 ± 0.003	0.058 ± 0.003	0.061 ± 0.003	0.059 ± 0.003
Relative	1.615 ± 0.097	1.672 ± 0.109	1.888 ± 0.104	1.881 ± 0.079

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate[a]

	0 mg/L	80 mg/L	400 mg/L	800 mg/L
Male				
n	9	8	8	9
Necropsy body wt	50.7 ± 1.4	52.7 ± 1.2	51.0 ± 1.5	51.8 ± 1.4
Heart				
Absolute	0.249 ± 0.009	0.253 ± 0.009	0.285 ± 0.009*	0.237 ± 0.013
Relative	4.939 ± 0.210	4.802 ± 0.143	5.633 ± 0.264	4.575 ± 0.228
R. Kidney				
Absolute	0.328 ± 0.017	0.312 ± 0.013	0.367 ± 0.022	0.327 ± 0.018
Relative	6.461 ± 0.249	5.933 ± 0.235	7.173 ± 0.307	6.330 ± 0.359
Liver				
Absolute	3.353 ± 0.196	3.567 ± 0.163	3.240 ± 0.242	3.265 ± 0.222
Relative	65.694 ± 2.560	67.629 ± 2.237	62.981 ± 3.408	62.754 ± 3.526
Lung				
Absolute	0.253 ± 0.022	0.256 ± 0.017	0.276 ± 0.018	0.233 ± 0.006
Relative	4.981 ± 0.390	4.871 ± 0.334	5.377 ± 0.265	4.520 ± 0.149
R. Testis				
Absolute	0.106 ± 0.009	0.109 ± 0.005	0.117 ± 0.005	0.111 ± 0.004
Relative	2.103 ± 0.182	2.071 ± 0.070	2.302 ± 0.107	2.140 ± 0.085
Thymus				
Absolute	0.046 ± 0.006	0.041 ± 0.003	0.040 ± 0.002	0.046 ± 0.004
Relative	0.895 ± 0.097	0.776 ± 0.047	0.786 ± 0.047	0.880 ± 0.063
Female				
n	9	9	10	10
Necropsy body wt	47.7 ± 2.8	45.7 ± 2.4	38.3 ± 2.7*	42.9 ± 2.1
Heart				
Absolute	0.191 ± 0.008	0.188 ± 0.008	0.203 ± 0.010	0.186 ± 0.008
Relative	4.069 ± 0.189	4.211 ± 0.318	5.408 ± 0.254**	4.371 ± 0.159
R. Kidney				
Absolute	0.233 ± 0.005	0.234 ± 0.005	0.229 ± 0.008	0.225 ± 0.008
Relative	5.015 ± 0.289	5.247 ± 0.332	6.207 ± 0.421*	5.301 ± 0.197
Liver				
Absolute	1.955 ± 0.073	1.840 ± 0.084	1.967 ± 0.163	1.895 ± 0.067
Relative	41.507 ± 1.282	40.637 ± 1.450	54.271 ± 7.518	44.651 ± 1.461
Lung				
Absolute	0.240 ± 0.020	0.237 ± 0.011	0.254 ± 0.021	0.271 ± 0.014
Relative	5.072 ± 0.313	5.347 ± 0.442	7.108 ± 1.025	6.417 ± 0.369
Thymus				
Absolute	0.048 ± 0.008	0.040 ± 0.003	0.121 ± 0.078	0.045 ± 0.004
Relative	1.032 ± 0.180	0.907 ± 0.077	4.002 ± 2.890	1.045 ± 0.086

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

APPENDIX G
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

Sodium Bromate

Sodium bromate was obtained from Fisher Scientific (Fairlawn, NJ) in one lot (946272A) that was used in the 26- and 39-week dermal studies and in the 27- and 43-week drinking water studies. Identity and purity analyses were conducted by the analytical chemistry laboratories, Research Triangle Institute (RTI) (Research Triangle Park, NC) and Battelle Memorial Institute (Columbus, OH), and by the study laboratory, Battelle Columbus Operations (Columbus, OH). Reports on analyses performed in support of the sodium bromate studies are on file at the National Institute of Environmental Health Sciences.

Lot 946272A, a white crystalline powder, was identified as sodium bromate by the analytical chemistry laboratories and by the study laboratory using infrared spectroscopy (IR), by Galbraith Laboratories, Inc. (Knoxville, TN), using elemental analysis, and by Battelle Memorial Institute using inductively coupled plasma emission (ICP) spectrometry for elemental sodium content. All IR spectra were consistent with the structure and with a literature spectrum of sodium bromate. An IR spectrum is presented in Figure G1. Elemental analyses for bromine and sodium were in agreement with the theoretical values for sodium bromate. ICP spectrometry indicated that the sodium content was 93.5% of theoretical.

The purity of lot 946272A was determined by the analytical chemistry laboratories and by the study laboratory using ion chromatography (IC) and by Battelle Memorial Institute using iodometric titration of bromate ions. The IC system was operated in anion mode to measure the bromate anion and utilized a dual pump ion chromatograph, an IonPac® AS12A column (200 mm × 4 mm), a CDM-1 suppressed conductivity detector from Dionex Corp. (Sunnyvale, CA), and an isocratic mobile phase of 2.7 mM sodium carbonate/0.3 mM sodium bicarbonate at a flow rate of 1.5 mL/minute. Iodometric titration utilized certified 0.1 N sodium thiosulfate solution and a starch indicator to measure the iodine produced from the oxidation of iodide ion by bromate.

For lot 946272A, IC indicated one major peak and no impurities with relative areas greater than 0.1%, with purities of 101.2% relative to a frozen reference standard and 97% based on bromate anion recovery relative to a reference sample of 99% purity obtained from Aldrich Chemical Co. (Milwaukee, WI). Iodometric titration indicated a purity of approximately 99%. The overall purity of lot 946272A was determined to be 99% or greater.

To ensure stability, the bulk chemical was stored at room temperature, protected from light. Stability was monitored during the 26-, 27-, 39-, and 43-week studies using IC by a system similar to that described for purity analysis. No degradation of the bulk chemical was detected.

12-*O*-Tetradecanoylphorbol-13-acetate

12-*O*-tetradecanoylphorbol-13-acetate (TPA) was obtained from Sigma-Aldrich Chemical Company (St. Louis, MO) in one lot (48H1178) that was used in the 26- week and 27-week studies in Tg.AC hemizygous mice. Lot 48H1178, a white crystalline powder, was identified as TPA by RTI using IR and proton nuclear magnetic resonance (NMR) spectrometry. All spectra were consistent with the structure of TPA.

The purity of lot 48H1178 was determined by RTI using high performance liquid chromatography (HPLC). HPLC analysis was performed with a Dupont Zorbax Rx C8 column (25 cm × 4.6 mm; Agilent Technologies, Palo Alto, CA), photodiode array detection monitored at 232 nm, and an isocratic mobile phase of water:acetonitrile (10:90)

with a flow rate of 1.0 mL/minute. Analysis indicated one major peak and one impurity peak with an area equal to approximately 0.11% of the total integrated peak area. The overall purity of lot 48H1178 was determined to be greater than 99%.

Ethanol

USP-grade 95% ethanol was obtained from Spectrum Chemicals and Laboratory Products (Gardena, CA) in one lot (NK0283) that was used in the 26- and 39-week dermal studies. Lot NK0283, a clear liquid, was identified as ethanol by the study laboratory using IR; the IR spectrum was consistent with a literature spectrum (*Aldrich*, 1985) of ethanol.

The purity of lot NK0283 was determined by the study laboratory using gas chromatography (GC). The analytical system used a Fisons gas chromatograph (Carlo Erba/Fisons, Ltd, Valencia, CA) with a DB-Wax column (30 m × 0.53 mm, 1.0-µm film thickness; Agilent Technologies, Palo Alto, CA), a flame ionization detector, helium carrier gas flowing at approximately 10 mL/minute, and an oven temperature program of 80° C for 5 minutes, then 10° C/minute to 220° C, and held for 3 minutes. Analysis indicated one major peak and no impurities with areas greater than or equal to 0.1% of the major peak. The overall purity of lot NK0283 was determined to be greater than 99%.

The purity of the bulk chemical was periodically monitored by the study laboratory during the studies using the GC system described above. No degradation of the ethanol was detected.

Preparation and Analysis of Dose Formulations

Dermal Studies

The dose formulations were prepared every 4 to 5 weeks by mixing sodium bromate and 40% USP-grade 95% ethanol/60% deionized water to give the required concentrations (Table G1). The dose formulations of sodium bromate were stored at room temperature in clear glass bottles for up to 35 days. A positive control dose formulation of TPA was prepared twice during the studies by adding the appropriate amount of TPA to acetone; the formulations were stored at approximately 5° C in amber glass bottles for up to 6 months.

Stability studies of a 5.67 mg/mL dose formulation were conducted by RTI using IC by a system similar to that described for purity determination. Stability was confirmed for at least 35 days for dose formulations stored in 100 mL glass bottles at temperatures up to ambient, for at least 3 hours for dose formulations stored in capped, partially filled clear glass scintillation vials, and for at least 24 hours for dose formulations stored exposed to light and air at 25° C to 30° C followed by resolubilization in 40% USP-grade 95% ethanol/60% deionized water. Stability studies of a positive control dose formulation of TPA were conducted by RTI using HPLC by a system similar to that described for purity determination. Stability was confirmed for at least 6 months for formulations stored in amber glass bottles at approximately 5° C.

Periodic analyses of the dose formulations of sodium bromate were conducted by the study laboratory using IC by a system similar to that described for purity determination. During the 26- and 39-week studies, dose formulations were analyzed four times; all 12 of the dose formulations for Tg.AC hemizygous mice were within 10% of the target concentrations (Table G2). Animal room samples of these dose formulations were also analyzed; four of six animal room samples were within 10% of the target concentrations.

Drinking Water Studies

The dose formulations were prepared every 2 to 5 weeks by adding a specified amount of sodium bromate to tap water in a calibrated NALGENE® tank and stirring with an overhead drum stirrer until dissolved (Table G1). The dose formulations of sodium bromate were stored at room temperature for up to 35 days in the NALGENE® tanks

in which they were mixed. A positive control dose formulation of TPA was prepared and stored as described for the dermal studies.

Stability studies of a 5.67 mg/mL dose formulation were conducted by RTI using IC by a system similar to that described for purity determination. Stability was confirmed for at least 35 days for dose formulations stored in 100 mL glass bottles at temperatures up to ambient, and for at least 7 days in partially filled 500 mL clear glass drinking bottles.

Periodic analyses of the dose formulations of sodium bromate were conducted by the study laboratory using an IC system similar to that described for analyses of the dermal formulations of the chemical except that a Dionex IonPac® AS9SC column (200 mm × 4 mm) was used and the isocratic mobile phase was 5.4 mM sodium carbonate/0.6 mM sodium bicarbonate. During the 27- and 43-week studies, these dose formulations were analyzed four times; all 13 of the dose formulations for Tg.AC hemizygous and p53 haploinsufficient mice were within 10% of the target concentrations (Table G3). Animal room samples of these dose formulations were also analyzed; all 12 animal room samples (six for Tg.AC hemizygous mice and six for p53 haploinsufficient mice) were within 10% of the target concentrations. No sodium bromate was found in control formulations above a method detection limit of 0.45 mg/L.

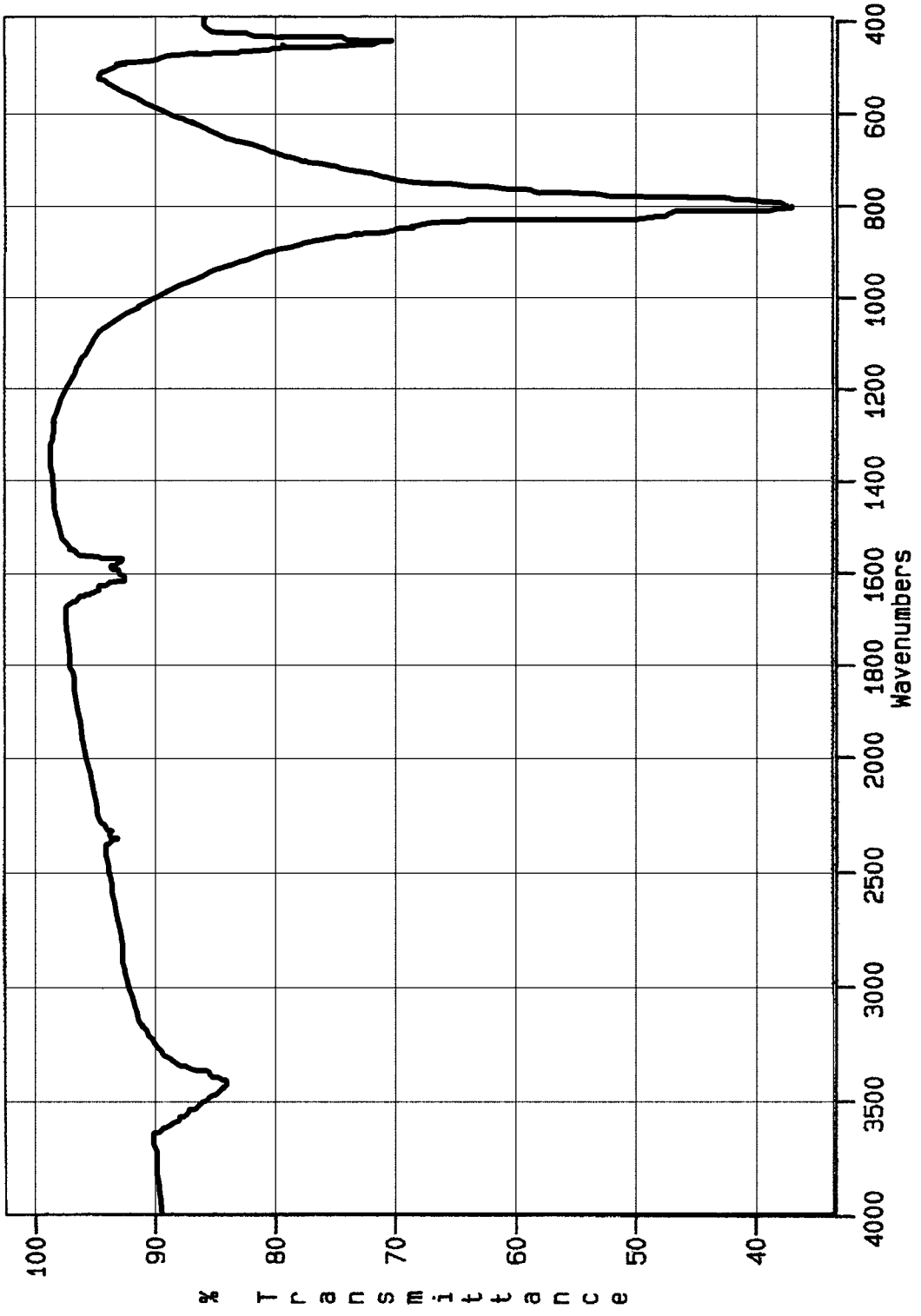

FIGURE G1
Infrared Absorption Spectrum of Sodium Bromate

TABLE G1
Preparation and Storage of Dose Formulations in the Dermal and Drinking Water Studies of Sodium Bromate

	Dermal Studies	Drinking Water Studies
Preparation	Sodium bromate: A specified amount of sodium bromate was added to 150 mL of deionized water in a 250 mL volumetric flask. The flask was sealed, shaken, and sonicated until sodium bromate was dissolved. The solution was diluted to volume with USP-grade 95% ethanol, sealed, shaken, and stirred with a stir bar for approximately 30 minutes and inverted at least 10 times. Dose formulations were prepared every 4 to 5 weeks.	Sodium bromate: A specified amount of sodium bromate was added to 48 or 120 L of tap water in a calibrated NALGENE® tank and stirred with an overhead drum stirrer for 15 minutes or until the sodium bromate dissolved. Dose formulations were prepared every 2 to 5 weeks.
	TPA: A 12.5 µg/mL formulation was prepared by diluting the appropriate amount of TPA in acetone. Formulations were prepared twice during the study.	TPA: A 12.5 µg/mL formulation was prepared by diluting the appropriate amount of TPA in acetone. Formulations were prepared twice during the studies.
Chemical Lot Number	Sodium bromate: 946272A TPA: 48H1178	Sodium bromate: 946272A TPA: 48H1178
Maximum Storage Time	Sodium bromate: 35 days TPA: 6 months	Sodium bromate: 35 days TPA: 6 months
Storage Conditions	Sodium bromate: Formulations were transferred to 250-mL clear glass bottles, sealed with Teflon®-lined lids, and stored at room temperature.	Sodium bromate: Formulations remained in the NALGENE® containers in which they were prepared; the lids were sealed with Parafilm or tape and the containers were stored at room temperature.
	TPA: Stored in amber glass bottles sealed with Teflon®-lined lids and refrigerated at approximately 5° C.	TPA: Stored in amber glass bottles sealed with Teflon®-lined lids and refrigerated at approximately 5° C.
Study Laboratory	Battelle Columbus Operations (Columbus, OH)	Battelle Columbus Operations (Columbus, OH)

TABLE G2
Results of Analyses of Dose Formulations Administered to Tg.AC Hemizygous Mice in the 26- and 39-Week Dermal Studies of Sodium Bromate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	Difference from Target (%)
October 18, 1999	October 19, 1999	19.4	19.54	+1
		38.8	40.06	+3
		77.6	75.10	–3
	November 29-30, 1999[b]	19.4	22.15	+14
		38.8	46.09	+19
		77.6	72.14	–7
January 10, 2000	January 11, 2000	19.4	19.34	0
		38.8	39.56	+2
		77.6	78.38	+1
April 5, 2000	April 6-7, 2000	19.4	18.74	–3
		38.8	40.00	+3
		77.6	71.22	–8
June 26, 2000	June 28, 2000	19.4	20.11	+4
		38.8	39.52	+2
		77.6	73.01	–6
	August 2, 2000[b]	19.4	19.91	+3
		38.8	41.03	+6
		77.6	81.48	+5

[a] Results of duplicate analyses. Dosing volume=3.3 mL/kg; 19.4 mg/mL=64 mg/kg, 38.8 mg/mL=128 mg/kg, 77.6 mg/mL=256 mg/kg.
[b] Animal room samples

TABLE G3
Results of Analyses of Dose Formulations Administered to Tg.AC Hemizygous Mice and p53 Haploinsufficient Mice in the 27- and 43-Week Drinking Water Studies of Sodium Bromate

Date Prepared	Date Analyzed	Target Concentration (mg/L)	Determined Concentration[a] (mg/L)	Difference from Target (%)
Tg.AC Hemizygous Mice and p53 Haploinsufficient Mice				
September 13, 1999	September 16, 1999	80	75.08	–6
		400	397.3	–1
		800	807.2	+1
December 7, 1999	December 8, 1999	80	77.81	–3
		400	403.2	+1
		800	821.2	+3
		800	816.1	+2
February 29, 2000	February 29, 2000	80	77.40	–3
		400	408.9	+2
		800	816.3	+2
May 19, 2000	May 24, 2000	80	78.29	–2
		400	412.5	+3
		800	825.8	+3
Animal Room Samples				
Tg.AC Hemizygous Mice				
September 13, 1999	October 19, 2000	80	73.51	–8
		400	397.2	–1
		800	797.4	0
May 19, 2000	June 28-29, 2000	80	76.69	–4
		400	413.7	+3
		800	810.1	+1
p53 Haploinsufficient Mice				
September 13, 1999	October 19, 1999	80	74.34	–7
		400	397.4	–1
		800	793.7	–1
May 19, 2000	June 28-29, 2000	80	76.21	–5
		400	406.1	+2
		800	806.2	+1

[a] Results of duplicate analyses

APPENDIX H
WATER AND COMPOUND CONSUMPTION IN THE 27- AND 43-WEEK DRINKING WATER STUDIES OF SODIUM BROMATE

TABLE H1
Water and Compound Consumption by Male Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	6.0	24.1				6.2	24.0	104	5.0	23.9	166
3	5.8	26.2	5.4	26.4	16	4.2	26.0	64	4.6	25.3	144
4	4.8	27.6				4.7	27.4	69	5.8	26.9	173
5	6.4	28.3	5.7	29.1	16	4.5	28.6	63	5.0	27.4	147
6	5.5	29.7	4.9	30.0	13	5.1	29.3	70	4.0	28.0	115
7			5.5	30.7	14	4.9	29.9	65	5.8	28.6	161
8	6.2	31.7	4.3	31.3	11	5.5	30.4	72	5.2	28.7	144
9	5.3	32.6	4.7	32.4	12	5.0	31.4	63	5.3	29.6	144
10	7.3	33.3	5.8	33.0	14	5.0	31.7	63	4.7	29.2	129
11	5.4	34.9	5.8	34.5	13	5.2	32.3	64	5.6	30.1	150
12	5.4	35.9	5.0	35.0	11	6.7	33.1	81	4.7	30.8	121
13	4.5	36.5	4.8	35.9	11	6.2	34.2	73	4.9	31.1	126
14	4.6	36.5	5.3	36.2	12	4.8	33.6	57	4.2	30.6	109
15	5.0	36.3	5.7	35.8	13	5.4	35.0	62	4.8	31.7	121
16	5.2	35.7							4.9	31.7	124
17	4.8	35.8	6.6	35.6	15				3.9	31.0	100
18	5.4	36.2	5.7	35.8	13	5.1	33.0	62	4.5	30.8	116
19	5.5	36.2	4.6	35.4	10	3.7	33.3	44	4.0	30.6	105
20	4.9	36.4	6.9	36.0	15	4.1	33.1	50	3.4	31.2	87
21	5.0	36.6	5.7	36.6	13	4.1	33.6	48	5.5	31.2	87
22	4.7	37.1	5.5	37.0	12	5.7	33.9	68	5.4	31.5	136
23	4.7	36.4	5.2	37.2	11	5.6	33.3	67	4.5	30.9	115
24	5.2	37.0	5.0	37.6	11	4.7	34.3	54	4.2	31.1	108
25	5.1	36.2	4.4	37.6	9	3.6	33.9	42	4.4	31.7	111
26	4.9	38.0	4.0	37.1	9	4.0	34.0	48	4.4	32.1	111
Mean for weeks											
1-13	5.7	31.0	5.2	31.8	13	5.3	29.9	71	5.0	28.3	143
14-26	5.0	36.5	5.4	36.5	12	4.6	33.7	55	4.5	31.3	114

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

TABLE H2
Water and Compound Consumption by Female Tg.AC Hemizygous Mice in the 27-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2						5.5	20.0	111			
3	5.3	20.3				5.4	21.4	101	4.7	21.0	179
4	6.1	22.6	5.2	22.9	18	4.4	23.2	75	4.5	22.4	160
5	6.2	23.5	4.5	23.6	15	4.8	24.1	80	4.3	22.8	149
6	5.8	23.8	5.5	24.0	18	5.7	23.8	95	4.2	22.4	148
7	4.5	25.0	5.0	24.5	16	4.2	24.5	69	4.6	23.7	157
8	5.7	25.3	5.4	25.3	17	5.3	25.1	85	4.6	24.1	154
9	5.1	26.4	5.4	26.0	17	5.6	25.8	87	4.7	25.0	149
10	5.5	27.6	5.1	26.4	15	5.6	26.2	85	4.7	24.3	155
11	4.9	28.0	4.8	26.2	15	5.1	26.0	78	5.0	25.5	156
12	5.0	28.4	5.0	27.2	15	5.8	26.7	86	4.1	25.5	128
13	5.3	28.3	5.4	27.6	16	4.6	26.9	69	4.8	25.5	150
14	5.2	28.4	4.8	27.7	14	4.2	27.3	61	4.2	25.6	133
15	3.8	28.9	4.3	27.4	12	5.0	27.7	72	4.3	26.0	132
16	3.5	28.7	5.8	27.7	17	4.6	27.2	68	5.8	26.2	178
17	5.4	29.0	4.6	27.7	13	5.1	27.2	75	4.4	25.2	138
18	4.3	28.7	3.3	27.4	10	5.0	27.8	71	5.0	26.1	152
19	3.4	28.2	4.8	28.0	14	4.2	28.9	58	4.2	25.4	134
20	4.7	29.1	5.3	29.0	15	4.4	29.2	61	5.1	25.8	159
21	4.6	29.6	4.9	29.3	13	3.9	29.5	53	4.0	25.8	125
22	4.5	30.9	5.5	29.7	15	4.5	30.3	59	5.3	26.6	159
23	3.5	29.8	4.5	29.4	12	3.7	30.1	49	4.6	26.6	138
24	3.2	30.6	4.3	29.4	12	3.4	31.0	44	4.4	26.2	136
25	3.3	31.4	3.6	29.8	10	4.0	31.2	51	4.3	26.6	130
26	3.8	31.2	4.3	30.5	11	3.1	31.8	39	4.3	26.5	129
Mean for weeks											
1-13	5.4	25.4	5.1	25.4	16	5.2	24.5	85	4.6	23.8	153
14-26	4.1	29.6	4.6	28.7	13	4.2	29.2	59	4.6	26.0	142

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

TABLE H3
Water and Compound Consumption by Male Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	4.3	24.4	4.2	24.3	14	4.3	24.8	69	6.2	23.2	214
3	5.3	25.9	5.0	25.0	16	4.7	26.1	73	5.0	24.1	167
4	4.7	28.2				4.6	28.4	64	6.2	25.8	191
5	5.7	29.0				5.0	29.3	68	4.6	27.4	135
6	5.9	29.4				4.7	30.6	62	4.3	28.7	119
7	5.7	30.9	4.0	31.7	10	5.6	30.8	73	5.1	29.4	138
8	5.8	32.1	6.0	32.4	15	6.4	31.8	80	4.4	29.7	119
9	5.5	32.5	5.8	33.1	14	5.9	32.1	73	5.3	30.6	140
10	6.0	33.4	4.9	34.2	11	5.7	32.6	69	4.8	30.5	127
11	4.9	33.3	7.1	33.9	17	5.1	32.8	62	4.2	30.1	113
12	4.0	34.3	6.1	35.0	14	4.6	33.2	56	4.6	30.3	121
13	3.7	35.1	5.5	36.0	12	5.1	33.9	60	5.1	30.7	133
14	3.9	35.6	4.8	36.5	10	5.1	34.2	60	5.1	30.4	135
15	4.3	36.2	4.5	37.5	10	4.9	34.9	56	4.9	30.4	129
16	3.9	34.8	6.7	36.7	14	3.9	33.9	46	4.9	30.2	131
17	4.9	36.2	5.5	37.1	12	4.7	34.3	55	3.8	31.4	98
18	5.6	36.8	6.9	37.7	15	4.1	34.8	47	5.0	31.6	128
19	3.9	36.7	5.4	36.3	12	5.2	34.5	60	4.9	32.1	122
20	4.7	36.8	4.3	37.6	9	4.3	35.8	48	4.4	32.6	108
21	4.8	37.1	3.8	37.2	8	4.6	36.0	51	5.2	32.2	130
22	5.6	38.1	3.5	37.2	8	5.0	36.0	56	5.5	32.1	137
23	4.4	37.8	4.2	36.7	9	4.5	36.5	49	5.8	31.4	147
24	3.9	37.8	3.6	36.6	8	4.5	35.6	50	4.7	31.4	121
25	5.1	37.7	3.8	36.5	8	3.9	35.8	44	5.2	31.6	132
26	4.3	38.7	4.3	37.5	9	4.0	36.2	44	4.6	32.2	114
27	3.4	38.3	4.0	37.4	8	4.8	35.8	54	4.2	32.3	104
28	4.4	39.6	3.6	37.2	8	4.9	38.8	50	3.8	33.0	91
29	4.7	39.2	4.7	40.2	9	3.8	37.5	41	4.3	32.7	106
30	3.9	38.4	4.7	39.5	10	4.1	37.2	44	4.1	32.9	99
31	4.4	38.0	7.0	40.2	14	3.4	37.6	37	4.1	32.5	100
32	4.7	37.9	4.7	39.9	9	4.2	37.8	45	3.8	33.1	92
33	3.6	39.3	5.5	40.9	11	3.9	38.1	41	4.8	33.6	115
34	4.1	39.1	6.2	40.8	12	3.3	37.0	35	4.9	33.6	117
35	4.3	42.7	3.9	41.2	8	2.8	37.7	30	4.9	32.3	120
36	4.2	42.6	5.0	41.9	10	3.4	37.7	36	4.8	32.5	117
37	6.4	42.5	6.9	41.7	13	3.4	39.6	35	5.0	32.3	123
38	3.5	42.6	6.7	41.0	13	3.3	39.3	34	5.8	30.6	152
39	4.2	43.2	3.8	42.7	7	4.2	38.6	43	5.3	30.1	140
40	3.9	43.8	4.7	42.0	9	4.5	39.1	46	6.1	29.0	168
41	3.0	43.0	5.7	42.2	11	5.0	40.7	49	6.5	29.0	179
42	4.6	42.1	6.5	42.1	12	3.6	40.6	35	6.4	29.9	170
Mean for weeks											
1-13	5.1	30.7	5.4	31.7	14	5.1	30.5	67	5.0	28.4	143
14-42	4.4	39.1	5.0	39.0	10	4.2	36.9	45	4.9	31.7	125

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

TABLE H4
Water and Compound Consumption by Female Tg.AC Hemizygous Mice in the 43-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	6.4	19.6							4.2	19.3	175
3	5.2	20.3	4.6	20.6	18				4.5	21.7	165
4									4.1	22.7	145
5	5.6	23.9	7.0	23.7	24	6.7	23.8	113	3.9	23.4	133
6			6.7	24.6	22	6.7	24.6	109	3.5	24.1	116
7	5.7	24.6	6.4	25.1	20	6.5	24.8	104	3.9	24.4	128
8	4.3	26.2				4.3	25.7	66	3.9	24.9	125
9	5.1	25.0	6.0	26.2	18	4.3	25.7	68	4.0	25.2	128
10	5.8	25.6	6.8	26.3	21	3.8	26.0	58	3.9	25.1	123
11	4.5	25.3	4.9	26.3	15	4.5	25.2	71	4.2	24.6	137
12	4.0	25.8	5.6	26.6	17	4.4	26.2	67	3.7	24.6	120
13	5.0	25.8	7.1	27.1	21	4.3	27.1	63	3.8	24.1	126
14	4.3	26.1	5.6	27.4	16	5.5	27.0	81	3.5	24.0	118
15	5.3	27.6	5.4	28.5	15	5.2	27.4	75	4.9	25.2	154
16	5.6	28.5	3.6	27.4	11	3.9	26.8	58	5.8	24.6	187
17	5.2	28.8	5.2	28.1	15	4.7	28.2	66	4.9	24.9	159
18	5.4	28.9	4.9	29.2	14	6.0	29.0	83	6.5	27.0	193
19	4.6	30.4	4.3	29.6	12	4.6	30.0	61	6.3	26.4	190
20	4.0	29.5	5.1	29.7	14	4.0	30.1	54	6.6	26.4	200
21	5.1	30.2	4.9	30.1	13	3.9	29.8	53	6.1	26.4	185
22	3.4	30.5	5.3	29.7	14	6.0	28.3	84	5.8	26.5	175
23	4.6	29.8	5.7	29.9	15	5.0	28.6	70	5.7	25.9	178
24	4.6	32.1	5.3	29.5	14	5.3	29.9	70	4.8	25.2	151
25	4.9	31.8	3.3	29.7	9	3.2	30.3	42	5.4	25.9	168
26	4.7	32.1	4.8	29.5	13	5.1	31.7	64	4.4	26.0	135
27	4.8	33.8	5.4	29.2	15	4.6	32.1	57	4.5	26.6	135
28	4.0	34.0	4.4	30.3	12	5.1	32.8	62	3.7	27.1	110
29	4.3	34.2	5.1	29.9	14	5.6	33.3	67	4.1	26.4	123
30	4.2	33.4	4.8	30.0	13	4.7	34.2	55	4.4	27.2	128
31	4.5	33.4	4.1	29.7	11	4.7	34.4	55	5.4	27.8	156
32	4.8	33.6	5.0	29.8	13	4.1	33.6	49	5.6	28.3	160
33	4.6	34.6	4.5	29.5	12	4.4	34.8	51	5.3	28.3	149
34	4.1	35.3	4.2	28.9	12	4.2	35.2	48	4.5	27.4	131
35	3.5	34.9	4.4	28.3	13	3.7	34.8	42	5.2	28.8	145
36	3.2	34.8	4.7	29.7	13	4.9	35.6	54	4.9	28.3	139
37	4.9	35.3	3.8	29.1	11	4.8	36.2	53	5.2	28.5	145
38	4.2	35.1	5.1	29.4	14	4.4	35.6	50	5.6	28.7	155
39	4.2	34.8	4.1	29.5	11	4.1	35.1	47	4.7	26.9	140
40	4.7	34.7	4.8	29.8	13	2.9	35.1	33	5.7	24.0	191
41	3.9	33.9	4.6	29.2	13	3.6	33.9	43	6.3	23.6	212
42	4.7	33.6	4.3	29.4	12	4.2	37.8	44	6.2	23.1	215
Mean for weeks											
1-13	5.2	24.2	6.1	25.2	19	5.0	25.5	80	4.0	23.7	135
14-42	4.5	32.3	4.7	29.3	13	4.6	32.1	58	5.2	26.4	159

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

TABLE H5
Water and Compound Consumption by Male p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	3.6	25.0	3.6	25.7	11	3.3	25.6	52	3.4	24.6	110
3	3.6	26.2	3.5	26.8	10	3.4	27.0	50	3.2	25.9	100
5	3.7	28.4	3.7	29.3	10	3.5	29.5	47	3.4	28.2	97
6	3.5	29.7	3.4	30.9	9	3.4	31.1	44	3.2	29.6	87
7	3.7	31.3	3.7	32.8	9	3.6	32.7	44	3.3	30.9	86
8	3.7	32.2	3.5	33.8	8	3.4	34.2	40	3.3	31.8	82
9	4.0	33.5	3.8	34.9	9	3.7	35.4	42	3.5	33.3	84
10	3.8	35.1	3.5	36.4	8	3.5	36.7	38	3.1	34.5	73
11	3.9	36.4	3.5	37.7	8	3.6	37.9	38	3.2	35.5	72
12	4.1	37.7	3.6	38.9	7	3.6	39.1	37	3.2	36.4	70
13	4.1	38.7	3.6	40.0	7	3.7	39.9	37	3.3	37.4	70
14	4.0	39.9	3.5	40.9	7	3.5	40.1	35	3.2	38.0	68
15	4.1	41.2	3.5	42.2	7	3.5	41.3	34	3.2	38.8	67
16	4.2	41.6	3.7	43.0	7	3.7	41.6	36	3.3	39.0	67
17	4.1	42.2	3.9	43.3	7	3.7	42.2	35	3.2	40.7	62
18	4.2	43.1	3.9	44.9	7	3.8	42.9	36	3.4	41.5	66
19	4.1	43.6	3.6	44.9	6	3.7	43.3	34	3.2	42.0	61
20	4.2	44.0	3.9	45.1	7	3.8	45.4	33	3.4	42.6	63
21	4.1	44.4	3.6	45.7	6	4.1	45.8	36	3.3	42.8	62
22	4.3	44.5	3.9	46.6	7	3.9	46.1	34	3.5	43.7	64
23	4.3	45.3	3.8	47.4	6	3.9	46.4	34	3.2	44.4	57
24	4.2	45.6	3.9	47.6	7	4.2	46.8	36	3.4	45.1	60
25	3.9	46.3	3.7	48.0	6	4.0	47.4	34	3.1	45.7	54
26	4.4	46.5	4.1	48.1	7	3.9	47.2	33	3.4	45.5	60
Mean for weeks											
1-13	3.8	32.2	3.6	33.4	9	3.5	33.6	43	3.3	31.6	85
14-26	4.2	43.7	3.8	45.2	7	3.8	44.3	35	3.3	42.3	62

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

TABLE H6
Water and Compound Consumption by Female p53 Haploinsufficient Mice in the 27-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	4.0	20.8	3.9	20.5	15	4.0	20.3	79	3.9	20.4	154
3	4.3	21.4	3.9	21.2	15	4.0	21.1	77	3.9	21.0	148
5	4.5	22.6	4.4	22.3	16	4.5	21.7	82	4.3	22.1	156
6	4.6	23.0	4.0	22.8	14	4.1	22.2	75	4.2	22.4	148
7	4.3	23.8	4.1	23.4	14	4.3	22.7	75	4.1	23.1	142
8	4.6	24.2	4.3	23.8	14	4.1	22.9	72	4.4	23.1	153
9	4.8	24.9	4.2	24.4	14	4.6	23.5	78	4.3	23.4	148
10	4.6	25.6	3.9	25.2	12	4.3	24.2	72	3.8	24.0	128
11	4.9	26.2	3.9	25.5	12	4.4	24.3	72	4.2	24.0	141
12	4.9	26.2	4.2	26.0	13	4.6	24.8	74	4.6	24.2	152
13	4.8	27.4	4.4	26.9	13	4.8	24.8	77	4.6	24.6	148
14	4.6	28.0	4.3	27.1	13	4.8	25.9	75	4.4	25.1	141
15	4.6	28.4	4.2	27.6	12	4.9	26.4	73	4.7	25.5	147
16	4.9	29.3	4.3	28.4	12	4.5	26.9	67	4.4	26.1	135
17	4.6	30.4	4.1	29.2	11	4.7	27.5	69	4.2	26.8	124
18	4.5	30.2	4.3	28.9	12	4.6	27.7	67	4.2	27.0	126
19	4.6	30.5	4.1	28.8	11	4.1	28.0	59	4.5	27.0	133
20	4.7	30.8	4.5	29.7	12	4.6	28.5	65	4.4	27.2	128
21	4.5	31.3	4.2	30.3	11	4.7	29.0	65	4.4	27.5	128
22	4.7	31.3	4.4	31.0	11	4.8	30.1	64	4.4	28.4	123
23	4.4	32.4	4.0	31.9	10	4.6	31.1	59	3.8	29.6	102
24	4.3	32.8	4.5	33.0	11	4.5	31.8	57	3.8	29.3	104
25	4.3	33.6	4.2	33.8	10	4.4	32.6	54	3.9	29.9	104
26	4.5	34.3	4.1	33.7	10	4.7	33.2	56	4.2	30.3	111
Mean for weeks											
1-13	4.6	24.2	4.1	23.8	14	4.3	23.0	76	4.2	22.9	147
14-26	4.5	31.0	4.2	30.3	11	4.6	29.1	64	4.2	27.7	124

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

TABLE H7
Water and Compound Consumption by Male p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	3.5	25.6	3.4	25.4	10.8	3.5	25.9	53.4	3.2	24.5	103.4
3	3.4	27.2	3.8	26.8	11.4	3.5	27.3	50.9	3.2	26.2	98.4
5	3.5	29.2	3.6	28.7	10.0	3.5	29.5	46.8	3.4	28.5	94.5
6	3.4	30.8	3.5	29.8	9.3	3.4	30.7	44.5	3.3	29.8	87.2
7	3.6	32.7	3.8	31.8	9.5	3.5	32.7	43.0	3.4	31.8	86.4
8	3.5	33.7	3.5	33.0	8.6	3.5	33.9	41.6	3.2	32.8	78.0
9	3.5	34.7	3.6	33.8	8.5	3.4	33.3	40.3	3.2	33.6	76.6
10	3.5	35.9	3.6	35.3	8.2	3.5	35.0	40.5	3.2	34.6	74.6
11	3.4	37.2	3.6	36.7	7.9	3.5	36.7	38.7	3.0	35.2	69.2
12	3.3	38.6	3.5	36.7	7.7	3.3	37.5	35.7	3.1	36.2	69.5
13	3.5	39.9	4.2	38.6	8.6	3.8	39.0	38.5	3.2	37.3	69.0
14	3.3	40.6	3.8	40.0	7.6	3.5	40.0	35.3	3.1	38.3	65.6
15	3.5	42.0	3.9	41.1	7.6	3.4	41.0	33.6	3.2	39.5	65.4
16	3.6	42.5	3.9	42.0	7.5	3.6	41.7	34.9	3.4	40.0	68.9
17	3.8	43.6	3.9	42.8	7.4	3.7	42.4	34.8	3.4	40.5	67.1
18	3.6	44.3	4.2	44.0	7.6	3.8	43.0	35.0	3.5	41.3	68.4
19	3.7	45.3	4.1	44.8	7.4	3.9	43.9	35.5	3.4	42.2	64.9
20	3.6	45.8	3.9	45.1	6.9	3.9	44.3	34.9	3.4	43.0	62.9
21	3.5	46.3	3.9	45.8	6.7	3.9	44.9	34.6	3.3	43.7	61.0
22	3.5	46.7	4.1	46.3	7.1	3.9	45.3	34.1	3.3	44.1	59.4
23	3.4	46.8	3.8	45.9	6.6	4.0	46.0	34.4	3.3	44.8	58.5
25	1.8	47.5	2.0	47.7	3.3	2.0	47.3	16.8	1.5	46.4	26.1
26	3.6	48.4	3.6	47.3	6.0	4.1	48.0	34.0	3.3	47.2	55.8
27	3.7	48.1	4.0	48.1	6.7	4.1	47.8	34.0	3.2	46.7	54.3
28	3.9	49.5	3.9	49.3	6.4	4.4	48.9	36.1	3.6	47.6	60.5
29	3.6	49.3	3.7	49.0	6.1	3.9	48.9	32.2	3.4	47.9	56.3
30	3.6	49.5	4.0	48.4	6.6	4.1	49.0	33.8	3.5	48.2	58.9
31	3.6	49.8	3.7	47.7	6.2	4.1	49.5	33.0	3.5	48.7	57.2
32	3.9	50.1	3.8	49.8	6.2	4.2	48.8	34.2	3.4	47.2	57.9
33	3.6	50.4	3.8	50.2	6.0	4.1	49.6	33.3	3.4	48.6	56.2
34	3.5	50.1	3.8	50.5	6.1	4.0	48.9	33.1	3.2	48.5	52.9
35	3.5	49.2	3.7	50.4	5.9	4.2	49.5	34.2	3.2	48.9	51.9
36	3.8	49.6	4.0	50.8	6.4	4.2	50.1	33.5	3.2	49.5	51.8
37	4.0	50.4	3.9	50.6	6.2	4.2	50.3	33.6	3.4	50.2	54.6
38	3.9	50.2	4.1	51.3	6.4	4.2	50.8	33.2	3.4	50.5	53.7
39	3.9	50.2	4.1	51.4	6.3	4.1	51.0	32.4	3.3	50.5	52.1
40	4.0	50.0	4.2	52.1	6.4	4.3	51.5	33.5	3.5	51.2	54.0
41	4.3	51.8	4.2	52.6	6.4	4.5	50.8	35.6	3.5	51.7	53.9
42	4.1	51.4	4.3	52.5	6.5	4.7	50.9	37.2	3.4	51.2	53.2
Mean for weeks											
1-13	3.5	33.2	3.6	32.4	9.1	3.5	32.9	43.1	3.2	31.9	82.4
14-42	3.6	47.8	3.9	47.8	6.5	4.0	47.3	33.6	3.3	46.4	57.3

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

TABLE H8
Water and Compound Consumption by Female p53 Haploinsufficient Mice in the 43-Week Drinking Water Study of Sodium Bromate

Week	0 mg/L		80 mg/L			400 mg/L			800 mg/L		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Water (g/day)	Body Weight (g)	Dose (mg/kg)	Water (g/day)	Body Weight (g)	Dose (mg/kg)
2	3.7	20.5	3.8	20.4	15.0	3.7	20.0	73.9	3.6	19.8	145.2
3	4.5	21.2	4.2	21.6	15.6	4.0	20.7	77.4	3.7	21.1	138.9
5	4.8	22.1	4.2	23.0	14.5	4.0	22.0	72.3	4.2	22.3	149.9
6	4.4	22.5	3.8	23.4	13.0	4.0	22.0	71.9	4.2	22.2	149.7
7	4.4	23.1	4.3	23.9	14.3	3.9	22.4	69.1	4.0	23.0	138.5
8	4.8	23.6	4.0	24.0	13.3	3.9	22.5	69.1	4.3	23.2	147.2
9	4.2	23.4	4.0	24.4	13.1	4.0	22.7	71.4	4.4	23.4	149.4
10	4.5	24.2	4.2	24.6	13.7	4.2	23.3	71.9	4.1	23.9	135.7
11	4.1	24.9	4.2	25.3	13.2	4.1	23.4	69.6	4.1	24.5	135.4
12	4.1	25.7	4.2	25.9	12.9	4.0	23.8	66.6	3.8	24.7	122.2
13	4.6	26.4	4.2	27.0	12.4	4.3	24.7	69.5	4.3	25.4	135.1
14	4.8	27.0	4.2	27.3	12.2	4.1	24.4	67.7	4.1	25.6	127.1
15	4.8	27.6	4.6	27.7	13.3	4.2	24.6	69.2	4.4	26.1	133.4
16	4.8	28.8	4.5	28.5	12.6	4.2	25.3	65.9	4.0	26.9	118.5
17	4.9	29.7	4.3	29.3	11.7	4.4	25.7	68.1	4.1	27.3	121.4
18	5.0	30.5	4.6	30.4	12.1	4.2	26.5	63.7	4.4	28.3	123.3
19	5.1	31.1	4.3	31.5	10.8	4.3	27.1	64.2	4.1	28.7	115.0
20	4.6	31.7	4.7	32.5	11.5	4.3	27.5	62.1	4.0	28.6	112.0
21	4.8	32.5	4.4	33.0	10.7	4.5	28.5	63.7	4.1	29.3	112.5
22	4.7	33.2	4.3	33.4	10.3	4.3	28.3	60.2	4.1	29.9	110.1
23	4.5	33.8	4.0	33.3	9.6	4.1	29.3	56.1	3.8	30.9	98.6
25	2.3	35.9	2.1	35.3	4.8	2.0	30.3	26.4	1.8	32.0	44.2
26	4.7	36.6	4.6	35.4	10.5	4.1	31.5	51.6	3.9	33.1	93.2
27	4.8	37.1	4.6	37.0	9.9	4.2	31.9	52.6	4.0	33.6	94.0
28	4.7	38.9	4.6	38.6	9.4	4.5	33.4	54.2	4.0	35.0	91.0
29	4.7	38.5	4.4	38.8	9.1	4.1	33.5	48.9	3.8	35.3	86.8
30	4.8	39.0	4.6	39.5	9.2	4.1	33.1	50.0	4.0	36.1	87.7
31	4.6	39.8	4.6	40.2	9.1	4.1	33.5	48.3	3.6	36.8	78.5
32	5.2	40.7	4.7	40.5	9.2	4.5	34.9	51.3	3.8	37.0	82.9
33	4.5	41.3	4.4	41.1	8.6	4.0	35.3	45.7	3.4	36.2	74.1
34	4.4	42.2	4.7	42.2	8.9	3.9	35.0	44.3	3.6	37.6	76.6
35	4.2	42.4	4.4	42.7	8.3	4.1	35.9	46.1	3.5	38.0	73.8
36	4.4	43.4	4.2	43.5	7.7	4.2	36.8	45.8	3.8	39.0	78.7
37	5.2	44.5	4.6	44.5	8.2	4.1	37.9	43.0	3.6	39.5	73.8
38	4.4	45.2	4.9	44.0	8.8	4.1	37.6	43.9	3.7	40.5	73.5
39	4.4	44.6	4.7	44.3	8.4	4.3	37.9	45.2	3.6	40.8	70.2
40	4.7	44.1	4.7	44.4	8.4	4.7	38.9	48.1	3.8	41.5	73.0
41	4.5	45.0	4.7	46.1	8.1	4.2	38.9	43.6	3.7	42.2	69.4
42	4.6	47.4	4.5	46.1	7.9	4.3	38.6	45.1	3.5	42.1	66.3
Mean for weeks											
1-13	4.4	23.4	4.1	24.0	13.7	4.0	22.5	71.1	4.0	23.0	140.7
14-42	4.6	37.6	4.4	37.5	9.6	4.1	32.2	52.7	3.8	34.2	91.4

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