EPA/635/R-01/002

TOXICOLOGICAL REVIEW

OF

BROMATE

(CAS No. 15541-45-4)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

March 2001

U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Note: This document may undergo revisions in the future. The most up-to-date version will be made available electronically via the IRIS Home Page at *http://www.epa.gov/iris*.

CONTENTS—TOXICOLOGICAL REVIEW OF BROMATE (CAS No. 15541-45-4)

FOREWORD v
AUTHORS, CONTRIBUTORS, AND REVIEWERS vi

1. INTRODUCTION 1

2. CHEMICAL AND PHYSICAL PROPERTIES RELEVANT TO ASSESSMENTS 2

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS 4
   3.1. ABSORPTION 4
   3.2. DISTRIBUTION 4
   3.3. METABOLISM 5
   3.4. EXCRETION 5
   3.5. BIOACCUMULATION AND RETENTION 6
   3.6. SUMMARY 6

4. HAZARD IDENTIFICATION 6
   4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS 6
      4.1.1. Clinical Case Studies 6
      4.1.2. Summary 8
   4.2. PRECHRONIC/CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION 8
   4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES 15
   4.4. OTHER STUDIES 16
      4.4.1. Acute Toxicity Studies 16
      4.4.2. Carcinogenicity 17
      4.4.3. Genotoxicity 19
      4.4.4. Mechanistic Studies 20
   4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS 25
   4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION 26
   4.7. SUSCEPTIBLE POPULATIONS 30
      4.7.1. Possible Childhood Susceptibility 30
      4.7.2. Possible Gender Differences 30

5. DOSE-RESPONSE ASSESSMENTS 30
   5.1. ORAL REFERENCE DOSE 30
      5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification 30
      5.1.2. Method of Analysis—NOAEL/LOAEL 31
      5.1.3. RfD Derivation, Including Application of Uncertainty Factors and Modifying Factors 32

CONTENTS (continued)

5.2. INHALATION REFERENCE CONCENTRATION 32
5.3. CANCER ASSESSMENT 32
5.3.1. Choice of Critical Study: Rationale and Justification 32
5.3.2. Dose-response Data 33
5.3.3. Dose Conversion 34
5.3.4. Extrapolation Method 35
5.3.5. Slope Factor 38

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE 38
6.1. HAZARD CHARACTERIZATION 38
6.1.1. Characterization of Noncancer Hazard 38
6.1.2. Characterization of Carcinogenicity 39
6.2. DOSE-RESPONSE CHARACTERIZATION 40
6.2.1. Characterization of Noncancer Assessment 40
6.2.2. Characterization of Cancer Assessment 41

7. REFERENCES 43

Appendix A. External Peer Review—Summary of Comments and Disposition 47

LIST OF TABLES

Table 1. Physical and chemical properties of bromate 3
Table 2. Summary of tumor incidence in male rats 11
Table 3. Tumor incidence for male and female rats 12
Table 4. Tumor incidence in male rats 14
Table 5. Dose-response data 34
Table 6. Parameter estimates for one-stage Weibull time-to-tumor model 36
Table 7. Cancer potency estimates for bromate based on male rat tumors 36

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to bromate. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of bromate.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 202-566-1676.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

Chemical Manager/Author

Ambika Bathija
Office of Water
U.S. EPA

Contributing Authors

Joan S. Dollarhide, M.S., M.T.S.C., J.D.
Toxicologist
Toxicology Excellence for Risk Assessment
Cincinnati, OH

Jennifer Jinot
National Center for Environmental Assessment
Office of Research and Development, U.S. EPA

Reviewers

This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Economics, and Innovation; and the Regional Offices.

Internal EPA Reviewers

Jennifer Jinot
National Center for Environmental Assessment

Bruce Rodan
National Center for Environmental Assessment

Anthony DeAngelo
National Health and Environmental Effects Research Laboratory

External Peer Reviewers

Dr. Paul E. Brubaker
Brubaker and Associates

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

Dr. James Edward Klaunig
Division of Toxicology, Department of Pharmacology and Toxicology
Indiana University School of Medicine

Dr. June Dunnick
National Institute for Environmental Health Science

Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix A.

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in EPA's Integrated Risk Information System (IRIS).

The reference dose (RfD) and reference concentration (RfC) provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg-day. The *unit risk* is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000; 1 in 100,000; or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for bromate has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Proposed Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1995a), *Proposed Guidelines for Carcinogen Risk Assessment* (1996a), *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b), *Recommendations for and*

Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998); and memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, subject: Guidance on Risk Characterization.

Literature search strategies used for this compound were based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL PROPERTIES RELEVANT TO ASSESSMENTS

Sodium bromate and potassium bromate are white crystalline substances that are readily soluble in water (Budavari et al., 1989). Additional information regarding the physical and chemical properties of sodium and potassium bromate is presented in Table 1.

Sodium bromate is produced by the introduction of bromine into a solution of sodium carbonate. Sodium bromate is used in conjunction with sodium bromide to extract gold from gold ores. Bromate is also used in cleaning boilers and in the oxidation of sulfur and vat dyes (HSDB, 1991).

Potassium bromate is produced by passing bromine into a solution of potassium hydroxide. An industrial electrolytic process is used for large-scale production of potassium bromate (IARC, 1986).

Table 1. Physical and chemical properties of bromate

Property	Value	
	Sodium Bromate	**Potassium Bromate**
Chemical Abstracts Service No.	7789-38-0	7758-01-2
Registry of Toxic Effects of Chemical Substances No.	EF8750000	EF8725000
Synonyms	Bromic acid, sodium salt	Bromic acid, potassium salt
	$NaBrO_3$	$KBrO_3$
Molecular weight	150.90	167.01
Physical state and appearance	Odorless, white crystals	White crystals
Melting point	38°C	350°C
Boiling point	ND[a]	decomposes at 370°C
Density (17.5°C)	3.339 g/m^3	3.27 g/m^3
Solubility (water)	275 g/L at 0°C 909 g/L at 100°C	133 g/L at 40°C 497.5 g/L at 100°C
(organic)	Insoluble in alcohol	Slightly soluble in alcohol; insoluble in ether

[a] ND = no data.

Source: Adapted from Sax and Lewis, 1989; Weast, 1985.

Ozonation of waters containing bromide ion (Br^-) results in the oxidation of Br^- to hypobromous acid (HOBr) and further oxidation of the hypobromite ion (BrO^-) to (BrO_3^-) (Glaze, 1986; Haag and Holgne, 1983). Because the second step requires the hypobromite ion and does not proceed with the protonated form (HOBr), the rate of reaction increases with increasing pH, leveling off above the pK_a (8.8) of the acid. Bromate may be produced at a significant rate, even in dilute aqueous solution (Haag and Holgne, 1983). No information was located regarding 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 Holgne, 1983). Under continuous ozonation, conversion is quantitative.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

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 BrO_3^-/kg) intragastrically to male Wistar rats.[1] Approximately 30% of the dose was detected in the urine after 24 hours. After rats were dosed with 100 mg BrO_3^-/kg, it was detected in the plasma within 15 minutes.

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.

Lichtenberg et al. (1989) described the clinical course of a 2-year-old male (13 kg) with acute BrO_3^- poisoning. The child had ingested 1–2 ounces (30–60 mL) of a permanent wave solution containing 10–12 g BrO_3^-/100 mL. The child's estimated dose was 230–460 mg BrO_3^-/kg. Serum bromide levels peaked 12 hours after ingestion. The amount of bromide recovered from dialysate and urine was 1,850 mg, accounting for approximately 60%–70% of the bromate ingested.

No data are available regarding the absorption of bromate from the respiratory tract.

3.2. DISTRIBUTION

Studies in rats indicate that bromate appears in plasma and urine rapidly following ingestion. Oral gavage administration of 100 mg $KBrO_3$/kg to rats resulted in a peak plasma concentration 15 minutes after dosing and a peak urine concentration 1 hour after dosing. In addition, 24 hours after administration of $KBrO_3$, bromide was significantly ($p < 0.01$) increased in kidney (87.4 µg/g tissue), pancreas (32.1 µg/g tissue), stomach (113.5 µg/g tissue), small

[1] Information on the species, strain, and sex of animals is provided where available.

intestine (62.5 µg/g tissue), red blood cells (289.0 µg/g tissue), and plasma (187.1 µg/g tissue), indicating that bromate is distributed to several body tissues (Fujii et al., 1984).

No data are available regarding the distribution of bromate following inhalation exposure.

3.3. METABOLISM

Bromate is reduced to bromide in body tissues. Fujii et al. (1984) measured bromate levels in tissues of rats 24 hours after a single intragastric dose of 50 mg BrO_3^-/kg. Bromate was not detected (<5 µg/g) in any of the eight tissues analyzed, but significantly ($p < 0.01$) increased bromide levels for the plasma, red blood cells, pancreas, kidney, stomach, and small intestine of 187.1, 289.0, 32.1, 87.4, 113.5, and 62.5 µg/g tissue, respectively, were observed. Both bromate and bromide were significantly ($p < 0.01$) increased in the urine (1729.9 µg/mL and 1314.1 µg/mL, respectively). In vitro studies indicate that liver and kidney tissues degrade bromate to bromide and that glutathione (GSH) is probably involved in that degradation (Tanaka et al., 1984). However, Kutom et al. (1990) report that bromate is very stable in the body and only small amounts are reduced to bromide. Bromate may be converted to hydrobromic acid by the hydrochloric acid in the stomach (Kutom et al., 1990).

No data are available regarding the ability of bromate to cross the placenta. No data are available regarding the metabolism of bromate following inhalation exposure.

3.4. EXCRETION

Bromate is excreted mainly in the urine, partly as bromate and partly as bromide. Some bromate may also be eliminated in the feces (Fujii et al., 1984). Bromate was detected in the urine of rats following oral doses as low as 5 mg BrO_3^-/kg, and a dose-related increase in urinary bromate was reported for doses up to 100 mg/kg (Fujii et al., 1984). About 30% of an oral dose of 50 mg BrO_3^-/kg was recovered in the urine of rats as bromate 24 hours after administration.

No data are available regarding the excretion of bromate following inhalation exposure.

3.5. BIOACCUMULATION AND RETENTION

Small amounts of bromine (1–2 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).

3.6. SUMMARY

Bromate is rapidly absorbed from the gastrointestinal tract, at least in part unchanged. It is distributed throughout the body appearing in plasma and urine unchanged and in other tissues as bromide. Bromate is reduced to bromide in several body tissues, probably by GSH or other sulfhydryl-containing compounds. Most bromate is excreted in the urine, either as bromate or bromide, but some may leave the body in the feces. Bromine has been detected in adipose tissue of mice following long-term treatment with bromate.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS

No epidemiological studies were located on the effects of bromate exposure, and no data are available describing the effects of bromate in humans following inhalation exposure. 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. The most common acute signs are severe gastrointestinal irritation, central nervous system (CNS) depression, renal failure, and hearing loss. Representative case reports and several review articles are summarized below.

4.1.1. Clinical Case Studies

Several authors report the effects of acute oral exposure in children to potassium bromate following accidental ingestion of home permanent hair wave neutralizing solution (Benson, 1951; Parker and Barr, 1951; Quick et al., 1975; Gradus et al., 1984; Warshaw et al., 1985; Lue et al., 1988; Mack, 1988; Lichtenberg et al., 1989; Watanabe et al., 1992). The age of the children, when reported, ranged from 17 months (Gradus et al., 1984) to 6 years (Quick et al.,

1975). When estimated, doses ranged from 20 mg BrO_3^-/kg (Watanabe et al., 1992) to 1,000 mg BrO_3^-/kg (Lue et al., 1988). In all cases, the initial symptoms appeared to include abdominal pain, vomiting, or other gastrointestinal effects. CNS effects such as sedation, lethargy, and CNS depression appeared to be early symptoms of bromate poisoning after doses of about 70 mg/kg or higher (150 mg/kg, Parker and Barr, 1951; 70–700 mg/kg, Warshaw et al., 1985; 1,000 mg/kg, Lue et al., 1988; 230–460 mg/kg, Lichtenberg et al., 1989). Irreversible deafness is also an effect of bromate exposure (Quick et al., 1975; Gradus et al., 1984); one review of bromate ototoxicity found that deafness occurred in 18 of 31 cases, usually within 4–16 hours of exposure (Matsumoto et al., 1980).

Kidney effects were frequently observed in children following acute exposure, although a clear relationship does not exist between the dose and the development of renal effects. One review of bromate kidney toxicity found that renal failure occurred in 26 of 31 reported cases (Matsumoto et al., 1980). Anuria persisting for several days or longer was observed following exposure to 20 mg $KBrO_3$/kg (Quick et al., 1975) up to doses of 1,000 mg BrO_3^-/kg (Lue et al., 1988). In contrast, children ingesting 20 mg BrO_3^-/kg (Watanabe et al., 1992) and children ingesting 230–460 mg BrO_3^-/kg (Lichtenberg et al., 1989) did not demonstrate any renal effects. Histological examination of renal biopsies from children with renal effects indicated interstitial edema, interstitial fibrosis, tubular atrophy (Quick et al., 1975), and epithelial separation of the proximal tubules (Watanabe et al., 1992). Glomeruli were not affected.

Although there are fewer reports of acute oral exposure to bromate in adults (Matsumoto et al., 1980; Kuwahara et al., 1984; Kutom et al., 1990; Hamada et al., 1990), the symptoms of toxicity appear to be similar to those observed in children. When reported, the doses ingested ranged from 100 to 150 mg BrO_3^-/kg (Matsumoto et al., 1980) and to 500 mg $KBrO_3$/kg (Kuwahara et al., 1984). In all cases, the first symptoms to appear were gastrointestinal, including nausea, vomiting, diarrhea, and abdominal pain. Hearing loss was reported by three authors (Matsumoto et al., 1980; Kuwahara et al., 1984; Hamada et al., 1990). Anuria and renal failure were also reported (Kuwahara et al., 1984; Kutom et al., 1990; Hamada et al., 1990). The amount of time required to recovery renal function varied from 7 days (Kutom et al., 1990) to 5 weeks (Hamada et al., 1990), and in two cases, renal function was never restored (Kuwahara et al., 1984). Histological examination of renal biopsy (Kuwahara et al., 1984) demonstrated disrupted basement membranes, casts in proximal tubules, and tubular cell regeneration. Glomeruli were not affected.

4.1.2. Summary

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. The most common acute signs are severe gastrointestinal irritation (vomiting, pain, and diarrhea) and CNS depression (lethargy, hypotension, hypotonicity, and loss of reflexes). Anemia from intravascular hemolysis may also occur. These effects are usually reversible. Later sequelae (usually within several days) include marked renal injury and hearing loss. Death from renal failure may ensue if medical intervention is not successful. If support is successful, renal function generally returns after 5–10 days. Hearing loss is usually irreversible. Estimated doses in these cases ranged from about 20 to 1,000 mg BrO_3^-/kg.

No epidemiological studies were located on noncarcinogenic or carcinogenic effects of bromate exposure in humans. No data were located on the effects of inhalation exposure in humans.

4.2. PRECHRONIC/CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

One subchronic study and several longer term studies evaluate the noncancer toxicity and carcinogenicity of bromate in animals following oral exposure. No studies were located that evaluated the health effects of bromate following inhalation exposure.

The subchronic effects of bromate were evaluated by Kurokawa et al. (1990), who administered potassium bromate in water at concentrations of 0, 150, 300, 600, 1,250, 2,500, 5,000, or 10,000 ppm to groups of F344 rats (10/sex/group) for 13 weeks. Assuming average default drinking water consumption of 0.4 L/day and an average default body weight of 0.3 kg, the authors calculated doses corresponding to these concentrations as about 0, 16, 32, 63, 140, 270, 650, or 1,080 mg BrO_3^-/kg-day. All animals exposed to >1,250 ppm died within 7 weeks. Observed signs of toxicity included significant inhibition of body weight gain in males at 600 ppm or above and significant increases of serum parameters (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen [BUN], Na^+, and cholinesterase) in both sexes at 600 ppm. Serum potassium

levels were significantly decreased.[2] Droplets of various sizes and regenerative changes in the renal tubules were observed. This study identifies 63 mg BrO_3^-/kg-day as an adverse effect level, but insufficient data were provided to determine whether effects occurred at lower doses.

Nakano et al. (1989) exposed male Wistar rats to 0.04% potassium bromate in drinking water for up to 15 months. At an intake of 0.1 L/kg-day, this corresponds to a dose of about 30 mg BrO_3^-/kg-day. Body weight gain was markedly inhibited in the exposed animals. Histological examination of kidneys at 7–11 weeks revealed karyopyknotic foci (a necrotic change characterized by shrinking of the nucleus and condensation of the chromatin) in tubules of the inner medulla. Increased BUN was noted after 15 months, along with marked structural abnormalities of the cortical tubules. On the basis of the decreased body weight gain and renal effects, this study identified a lowest-observed-adverse-effect-level (LOAEL) of 30 mg BrO_3^-/kg-day, but did not identify a no-observed-adverse-effect-level (NOAEL).

Kurokawa et al. (1983) investigated the carcinogenicity of potassium bromate in the drinking water of F344 rats. Potassium bromate was administered at concentrations of 0, 250, and 500 ppm for 110 weeks to F344 rats (53/sex/group). (Equivalent doses of bromate ion were approximately 12 and 33 mg BrO_3^-/kg-day, estimated from average reported body weights and water consumption.) However, growth of males in the high-dose group was severely inhibited, so the concentration was reduced to 400 ppm at week 60. Body weights were recorded weekly. At autopsy, blood was collected for hematological analysis. Organs were collected, weighed, and evaluated histopathologically. Body weight gain was significantly reduced in high-dose males, but not in the other treated groups. Survival was reduced in high-dose males by about week 60 and in low-dose males by about week 100. No effect on survival was observed in treated female rats. The first tumor was observed at 14 weeks in males and at 58 weeks in females. Therefore, animals surviving beyond these times were included in the analysis. Incidences of several tumor types were elevated in a dose-dependent manner (although not statistically significant) in treated rats, including thyroid (male and female), adrenal gland (male), large intestine (male and female), liver (male), and spleen (male). In male rats, the incidence of renal cell tumors (both adenocarcinomas and adenomas) and peritoneal mesotheliomas were statistically significantly increased in both dose groups compared with controls. In female rats, the incidence of renal cell tumors (both adenomas and adenocarcinomas) was statistically significantly increased in both treated groups compared with controls. A variety of noncancer effects were reported, including

[2] The level of statistical significance is $p < 0.05$ unless otherwise stated.

degenerative, necrotic, and regenerative changes in renal tubules; formation of hyaline droplets; thickening of transitional epithelium of renal pelvis; papillary hyperplasia; and papillary growth. The authors noted that the lesions were more extensive in degree and distribution in treated rats compared with controls, especially males. However, no information was provided on the incidence of these lesions or on the statistical significance of these findings, so a NOAEL for noncancer effects cannot be determined.

In a chronic study of bromate carcinogenicity, Kurokawa et al. (1986a) treated groups of 20–24 male F344 rats with water containing potassium bromate at 0, 15, 30, 60, 125, 250, or 500 mg/L for 104 weeks. The average doses for male rats were 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day, respectively. The weights of selected organs and all tumors were recorded. Histological examination of tissues only involved counting of neoplastic lesions. Compared with controls, the males in the high-dose group had decreased body weight gain and decreased survival, beginning at approximately week 70. Survival and body weight gain were comparable with controls for all remaining dose groups. The only nonneoplastic effect noted by the authors was a dose-related enhancement of the severity of nephropathic changes; however, no information was given on the doses at which these changes were observed.

Incidence of tumors and preneoplastic changes is summarized in Table 2. Statistically significantly increased incidence was observed for dysplastic foci at the 1.3 mg BrO_3^-/kg-day dose and above, for kidney tumors at the 5.6 mg BrO_3^-/kg-day dose and above, and for the thyroid tumors and mesotheliomas in the high-dose group only.

Kurokawa et al. (1986b) studied the carcinogenic potential of potassium bromate in both male and female F344 rats and female B6C3F1 mice. Potassium bromate was administered in drinking water. Time-weighted mean doses of potassium bromate were estimated by the authors on the basis of measured water consumption and body weight. The average bromate doses for rats were 0, 9.6, and 21.3 mg BrO_3^-/kg-day in males and 0, 9.6, and 19.6 mg BrO_3^-/kg-day in females. The average bromate doses for mice were 0, 43.5, and 91.6 mg BrO_3^-/kg-day. Parameters evaluated include body and organ weight, hematology, serum chemistry, and histopathology. Compared with controls, male rats in the high-dose group had a marked decrease in body weight gain and a decrease in survival, beginning approximately at week 70. The authors did not describe the cause of the decreased survival and body weight. For the low-dose groups in male rats and all dose groups in female rats and mice, survival and body weight gain were comparable to controls. Several nonneoplastic effects were described by the authors.

Table 2. Summary of tumor incidence in male rats

Lesion Type	Control	0.7 mg BrO_3^-/kg-day	1.3 mg BrO_3^-/kg-day	2.5 mg BrO_3^-/kg-day	5.6 mg BrO_3^-/kg-day	12.3 mg BrO_3^-/kg-day	33 mg BrO_3^-/kg-day
Dysplastic foci[a]	0/19	1/19 (5%)	5/20[b] (25%)	6/24[b] (25%)	12/24[c] (50%)	19/20[c] (95%)	19/20[c] (95%)
Kidney, adenoma, and carcinoma combined	0/19	0/19	0/20	1/24 (4%)	5/24[b] (21%)	5/20[b] (25%)	9/20[c] (45%; 3 carcinomas[d])
Thyroid, adenoma, and carcinoma combined	0/19	0/19	0/20	1/24 (4%)	0/24	3/20 (15%)	7/19[b] (37%)
Mesothelioma	0/19	0/19	3/20 (15%)	4/24 (17%)	2/24 (8%)	3/20 (15%)	15/20[b] (75%)

[a] Considered by the authors to be a preneoplastic lesion.
[b] Statistically significant when compared with control, $p < 0.05$.
[c] Statistically significant when compared with control, $p < 0.001$.
[d] Incidence of carcinomas alone not statistically significant.
Source: Kurokawa et al., 1986a.

Significant decreases in serum chemistry, including glutamate pyruvate transaminase, albumin-to-globulin ratio, potassium, and cholinesterase were observed in female rats in the high-dose group. Also, slightly increased BUN was observed in both male and female rats; dose groups were not specified. Degenerative and necrotic kidney lesions were observed in treated rats. Specific findings included hyaline casts in the tubular lumen, hyaline droplets, eosinophilic bodies, and brown pigments in the tubular epithelium. Again, however, the doses at which these changes were observed were not specified. No nonneoplastic changes in bromate-treated mice were discussed by the authors.

In Kurokawa et al. (1986b), treatment-related, statistically significant tumors observed in rats included renal cell adenomas and carcinomas and peritoneal mesotheliomas (in males only). The tumor incidence for rats is shown in Table 3. The authors note that "high incidence" of tumors was observed in the thyroid; however, this incidence was not statistically significant. In male rats, the earliest renal tumor was observed at 14 weeks and the earliest mesothelioma was observed at 72 weeks. In female rats, the earliest renal tumor was observed at 85 weeks. In female mice, no significant difference in tumor incidence between exposed and control animals was apparent after 78 weeks of dosing, based on histological examination of tissues at week 104. The authors concluded that potassium bromate was carcinogenic in rats of both sexes, but not in mice.

Table 3. Tumor incidence for male and female rats[a]

Tumor type	**Control**	**9.6 mg BrO_3^- /kg-day**	**19.6 (females) or 21.3 (males) mg BrO_3^- /kg-day**
Male rats			
Kidney, adenomas, and carcinomas combined	3/53 (6%)	32/53[b] (60%)	46/52[b] (88%)
Kidney, carcinomas alone	3/53 (6%)	24/53[b] (45%)	44/52[b] (85%)
Peritoneum, mesotheliomas	6/53 (11%)	17/52[c] (33%)	28/46[c] (61%)
Female rats			
Kidney, adenomas, and carcinomas combined	0/47	28/50[b] (56%)	39/49[b] (80%)
Kidney, carcinomas alone	0/47	21/50[b] (42%)	36/49[b] (73%)

[a]Incidence reported for the "effective number of rats," which is defined by the authors as the number of rats surviving longer than the time at which the earliest tumor of each type was observed.
[b]Statistically significant when compared with control, $p < 0.001$.
[c]Statistically significant when compared with control, $p < 0.01$.
Source: Kurokawa et al., 1986b.

In a recent study, U.S. EPA (DeAngelo et al., 1998) administered potassium bromate to male F344 rats and male B6C3F1 mice (78/group) in drinking water at concentrations of 0, 0.02,0.1, 0.2, and 0.4 g/L and 0, 0.08, 0.4, and 0.8 g/L, respectively, for 100 weeks. Time-weighted mean daily doses were calculated by the authors from the mean daily water consumption and the measured concentrations of potassium bromate. Bromate doses for the rats were 0, 1.1, 6.1, 12.9, and 28.7 mg BrO_3^-/kg-day. For rats, 6 animals/group were included for interim sacrifices, which occurred at 12, 26, 52, and 77 weeks. Parameters evaluated included survival, body weight, organ weight, serum chemistry, and histopathology.

In male rats, survival in the 28.7 mg BrO_3^-/kg-day dose group was decreased compared with controls, beginning at approximately week 79 (Wolf, 1998a); this decrease was statistically significant by study termination. In the 12.9 mg BrO_3^-/kg-day dose group, survival was decreased compared with controls, beginning at approximately week 88 (Wolf, 1998a); this decrease was also significant by study termination. Male rats in the 28.7 mg BrO_3^-/kg-day dose group also had a statistically significant decrease (18%) in the final mean body weight compared with controls. The decrease in survival and body weight were attributed to an excessive mesothelioma burden (Wolf, 1998a). The effects on survival and body weight in rats indicate that the maximum tolerated dose (MTD) was reached in this study.

In rats, water consumption was statistically significantly increased in the 12.9 and 28.7 mg/kg-day dose groups; the dose-related trend was also statistically significant. Rats in the 12.9 mg/kg-day dose group had increases, not statistically significant, in absolute and relative kidney weight and relative spleen weight. Rats in the 28.7 mg/kg-day dose group had statistically significant increases in relative liver weight, absolute and relative kidney weight, absolute and relative thyroid weight, and relative spleen weight. Nonneoplastic kidney lesions were observed in rats. Although the severity of chronic nephropathy was comparable between control and treated rats, there was a significant dose-dependent increase in the incidence of urothelial hyperplasia in rats in the 6.1 mg/kg-day and higher dose groups. The authors also observed foci of mineralization of the renal papilla and eosinophilic droplets in the proximal tubule epithelium, although they did not present any information on the dose levels for these findings. There were no other treatment-related nonneoplastic effects observed in any other tissue examined. On the basis of kidney effects in male rats, this study identifies a NOAEL of 1.1 mg BrO_3^-/kg-day and a LOAEL of 6.1 mg BrO_3^-/kg-day.

Tumor incidence for the terminal sacrifice in DeAngelo et al. (1998) is presented in Table 4. Statistically significant, dose-dependent increased tumor incidence was observed in the kidney (adenomas and carcinomas combined and carcinomas alone), the thyroid (adenomas and carcinomas combined and carcinomas alone), and *tunica vaginalis testis* (mesotheliomas). Based on data from the National Toxicology Program historical controls database (NTP, 1998), the historical control rates for these tumor types in male F344 rats are 0.6% for kidney renal tubule adenomas and carcinomas, 2.1% for thyroid follicular cell adenomas and carcinomas, and 1.5% for mesotheliomas. The earliest renal tumors and mesotheliomas in DeAngelo et al. (1998) were observed at 52 weeks; thyroid tumors were first seen at 26 weeks (Table 5, Section 5.3.2).

Results of DeAngelo et al. (1998) in male B6C3F1 mice indicate that mice may be less sensitive to the effects of bromate exposure than rats. Time-weighted mean daily doses were calculated by the authors from the mean daily water consumption and the measured concentrations of potassium bromate. Bromate doses for the mice were 0, 6.9, 32.5, and 59.6 mg BrO_3^-/kg-day. For mice, 7 animals/group were included for interim sacrifice, which occurred at 14, 31, 53, and 78 weeks. Bromate in drinking water had no effect on the survival, body weight, or organ weights of male mice. Mice in the 59.6 mg BrO_3^-/kg-day dose group had a statistically significant decrease in water consumption (17%) compared with controls. Serum chemistry results were comparable between controls and treated mice, and there was no increased incidence of nonneoplastic lesion in any tissue examined. Therefore, the highest dose tested,

Table 4. Tumor incidence in male rats

		Dose per group			
Tumor type	**Control**	**1.1 mg BrO_3^-/kg-day**	**6.1 mg BrO_3^-/kg-day**	**12.9 mg BrO_3^-/kg-day**	**28.7 mg BrO_3^-/kg-day**
Kidney, adenomas, and carcinomas combined	1/45 (2%)	1/43 (2%)	6/47 (13%)	3/39 (8%)	12/32[a,b] (38%)
Kidney, carcinomas alone	0/45	0/43	2/47 (4%)	1/39 (3%)	4/32[c,d] (13%)
Thyroid, adenomas, and carcinomas combined	0/36	4/39 (10%)	1/43 (2%)	4/35[c] (11%)	14/30[a,b] (47%)
Thyroid, carcinomas alone	0/36	2/39 (5%)	0/43	2/35 (6%)	6/30[b,c] (20%)
Mesothelioma	0/47	4/49 (8%)	5/49[c] (10%)	10/47[a] (21%)	27/43[a,b] (63%)

[a] Statistically significant when compared with control, $p < 0.002$.
[b] Statistically significant trend with dose, $p < 0.002$.
[c] Statistically significant when compared with control, $p < 0.05$.
[d] Statistically significant trend with dose, $p < 0.05$.
Source: DeAngelo et al., 1998.

59.6 mg BrO_3^-/kg-day, is a freestanding NOAEL in mice. The only type of tumor reported for male mice was kidney tumors; however, the incidence of adenoma and carcinoma combined was not dose dependent. Tumor incidence at terminal sacrifice for combined kidney tumors in male mice was 0/40, 5/38 ($p < 0.05$; 3 carcinomas), 3/41 (1 carcinoma), and 1/44 for the 0, 6.9, 32.5, and 59.6 mg BrO_3^-/kg-day groups, respectively.

Kurokawa et al. (1987) exposed male F344 rats (14–20/group) to water containing 500 ppm $KBrO_3$ (29.6–35.5 mg BrO_3^-/kg) for 13, 26, 39, or 52 weeks and studied the incidence of renal cell tumors at 104 weeks. The incidence of renal dysplastic foci, adenomas, and adenocarcinomas in rats exposed for 13–52 weeks was equal to or greater than that in rats receiving potassium bromate treatment continuously for 104 weeks (as reported in Kurokawa et al., 1987). The combined incidence of renal adenomas and adenocarcinomas was significantly higher in exposed animals than in controls ($p < 0.001$). The authors concluded that the minimum dose necessary for the induction of renal adenomas and adenocarcinomas was a cumulative dose of 4 g $KBrO_3$/kg (3.08 g BrO_3^-/kg), and the minimum treatment period for the induction of these tumors was 13 weeks. However, the authors also noted that the "true" minimum treatment time will be shorter than 13 weeks in experiments involving shorter exposure periods.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES

Limited data are available on the reproductive or developmental effects of bromate by the oral route. Only one screening-level study (Wolf and Kaiser, 1996) evaluates reproductive effects in rats. Although this study reports that pups were evaluated on postnatal day 5, no information on developmental endpoints is provided. No reliable multigenerational studies are available. Kurokawa et al. (1990) reports several multigenerational studies in which rats or mice were fed bread made from flour treated with potassium bromate. However, because most potassium bromate added to flour is converted to bromide during the bread baking process (Kurokawa et al., 1986b), it is unlikely that the animals in these multigenerational studies were actually exposed to bromate. No data are available evaluating reproductive or developmental effects by the inhalation route.

In a study conducted for NTP, Wolf and Kaiser (1996) evaluated the potential reproductive and developmental toxicity of sodium bromate in Sprague-Dawley rats following oral administration in the drinking water at concentrations of 0.25 ppm (2.6 mg/kg-day), 80 ppm (9.0 mg/kg-day), or 250 ppm (25.6 mg/kg-day) over a 35-day period. (Equivalent bromate ion doses are 2.2, 7.7, and 22 mg BrO_3^-/kg-day.) Two groups of female rats were treated. Group A

females (10/group) were dosed from study day 1 to 34 to test for effects during conception and early gestation. Group B females (13/group) were dosed from gestation day 6 to postnatal day 1 to test for effects during late gestation and birth. Male rats (10/group) were cohabited with Group B females for 5 days before dosing (study days 1–5) and were then dosed from study day 6 to day 34/35. Endpoints evaluated in males included clinical pathology, organ weight, sperm analysis, and histopathology. Endpoints evaluated in females included maternal body weight, number and weight of pups, and number of uterine implantations. Females in Group B were allowed to litter, and the pups were observed through postnatal day 5. However, there is no indication of the developmental endpoints that were evaluated in these pups or if any effects were observed. Treated males in the 250-ppm dose group demonstrated a statistically significant decrease (18%) in epididymal sperm density. All other endpoints evaluated were comparable between controls and treated groups. Female reproductive function was not adversely affected. There were no treatment-related gross or microscopic changes in the kidney, liver, spleen, testis, or epididymis. These results indicated that sodium bromate treatment did not produce any adverse signs of general toxicity in any of the dose levels tested; a MTD was not reached. On the basis of changes in sperm density, this study identifies a NOAEL of 80 ppm (7.7 mg BrO_3^-/kg-day) and a LOAEL of 250 ppm (22 mg BrO_3^-/kg-day).

4.4. OTHER STUDIES

4.4.1. Acute Toxicity Studies

Kurokawa et al. (1990) administered a single intragastric dose of potassium bromate to F344 rats, B6C3F1 mice, and Syrian golden hamsters (5/sex/group). Two-thirds of the animals in all species receiving high doses (700–900 mg/kg) died within 3 hours; the remaining animals receiving high doses died within 48 hours. LD_{50} values were higher for females than for males in all species and ranged from 280 mg/kg (male mice) to 495 mg/kg (female rats). Observed signs of toxicity included suppression of locomotion, ataxic gait, tachypnea, hypothermia, diarrhea, lacrimation, and piloerection. Hyperemia of the glandular stomach mucosa and lung congestion were observed in all species during necropsy. Kidney damage, evidenced by epithelial dilation and desquamation of the distal convoluted tubules, was observed in rats as early as 1 hour after treatment. Necrosis and degenerative and regenerative changes of the proximal tubular epithelium were also noted after longer exposure. These histological changes occurred later and were less severe in mice and hamsters.

Fujie et al. (1988) exposed male Long-Evans rats (50–100 g; 5/group) to single oral doses of 0, 1.0, 1.5, 2.0, or 3.0 mmol $KBrO_3$/kg (equivalent to 0, 129, 192, 257, and 385 mg BrO_3^-/kg, respectively). Six hours after the administration of the bromate, rats receiving the maximum dose (3.0 mmol; 385 mg BrO_3^-/kg) exhibited diarrhea and signs of sedation. The authors concluded that this was the maximum tolerance dose. No data were provided on presence or absence of clinical signs in the other dose groups. This study identified a LOAEL of 385 mg BrO_3^-/kg based on the appearance of diarrhea and lethargy in the exposed rats but did not identify a NOAEL.

Kurata et al. (1992) administered single intragastric doses of 0, 50, 300, 600, and 1,200 mg $KBrO_3$/kg (0, 38.5, 231, 462, and 924 mg BrO_3^-/kg, respectively) to 6-week-old male F344/NCr rats (5/group) as a preliminary test for a 104-week study of the tumor-initiating activity of potassium bromate. All rats treated with 1200 mg $KBrO_3$/kg (924 mg BrO_3^-/kg) and 4 of 5 rats treated with 600 mg $KBrO_3$/kg (462 mg BrO_3^-/kg) died within 24 hours. One animal from the 300 mg $KBrO_3$/kg (231 mg BrO_3^-/kg) dose group was found dead on day 6. Surviving animals were sacrificed at 4 weeks and all animals were necropsied. Significant increases in relative kidney weight were observed in animals in the 462 and 924 mg BrO_3^-/kg dose groups. Proximal tubule necrosis was observed in rats found dead during the study. In the 231 mg BrO_3^-/kg dose group, basophilic regeneration of the tubules and focal accumulation of eosinophilic droplets in the proximal tubules were observed, but not in the control group or in the 38.5 mg BrO_3^-/kg treatment group.

Kawana et al. (1991) administered 0, 100, 500, 1,000, 2,500, or 5,000 ppm $KBrO_3$ (0, 10.8, 54, 108, 270, and 540 mg BrO_3^-/kg-day, respectively) in drinking water to male SPF-ddy mice (9/group) for 2 weeks. Body weight gain was inhibited in the high-dose group (540 mg BrO_3^-/kg-day). Examination of the relative kidney, lung, and liver weights at necropsy revealed significant increases ($p < 0.05$) above the control organ weights, but dose-related changes were not observed. Alkaline phosphatase, γ-glutamyl transpeptidase, and -fetoprotein levels from the 270 and 540 mg BrO_3^-/kg-day dose groups were significantly increased ($p < 0.05$) compared with control animal levels, but only increases in γ-glutamyl transpeptidase levels appeared to be dose related.

4.4.2. Carcinogenicity

Matsushima et al. (1986) investigated the carcinogenicity of $KBrO_3$ administered subcutaneously to newborn rats and mice. Male and female newborn F344 rats and ICR mice

(24 hours old) were given single subcutaneous injections of 9.6, 19, 38, 77, or 154 mg BrO_3^-/kg. Another group of newborn rats and mice received four weekly injections of 9.6, 19, 38, 77, or 154 mg BrO_3^-/kg until weaning. Control animals received injections of olive oil. Rats were sacrificed at 82 weeks, mice were sacrificed at 78 weeks, and organs were examined histologically. No significant differences in the incidence of tumors in male or female rats or mice were observed. Under the conditions of the study, potassium bromate had no potential for carcinogenicity in newborn male or female rats or mice.

Kurata et al. (1992) tested the tumor initiation potential of bromate in a 104-week study in which male F344/NCr rats (29 or 39 per group) were given an intragastric dose of 300 mg $KBrO_3$/kg (231 mg BrO_3^-/kg), the maximum tolerated single dose. The rats were administered bromate alone, bromate followed by 4,000 ppm sodium barbital in the animal diet as a promoter, or sodium barbital in the diet alone. Sodium barbital was added to the diet starting 2 weeks after the animals were dosed with potassium bromate. Rats were examined at 30, 52, and 104 weeks for nephropathy. At 30 weeks, renal damage (dysplastic tubular foci) was evident in the rats exposed to potassium bromate followed by sodium barbital and in rats exposed to sodium barbital, but not in those exposed to potassium bromate alone. The results indicated that a single oral dose of 300 mg $KBrO_3$/kg (231 mg BrO_3^-/kg) administered to rats does not initiate renal tumors within a 104-week observation period.

Kurokawa et al. (1987) supplied groups of 8, 14, 20 and 26 male F344 rats with water containing 500 mg BrO_3^-/L for up to 104 weeks to assess the time-course of renal cell tumor induction. The average daily consumption of potassium bromate was 41.9 mg/kg (32.3 mg BrO_3^-/kg). At 104 weeks, the surviving animals were sacrificed and examined histopathologically for dysplastic foci, renal adenomas and adenocarcinomas, thyroid follicular cell tumors, and peritoneal mesotheliomas. All were significantly increased with continuous treatment. Dysplastic foci and renal adenomas were first observed following 26 weeks of continuous treatment. Renal dysplastic foci and adenomas were each significantly increased over controls by 52 weeks of treatment (mean number of renal cell tumors/rat was 0.81 vs. 0 in the controls). Continuous potassium bromate administration over 104 weeks resulted in renal adenocarcinomas in 3/20 (15%) and renal adenomas in 6/20 (30%) rats. At 104 weeks the mean number of renal cell tumors/rat was 1.25 compared with 0 in the controls. The combined incidence of follicular adenomas and adenocarcinomas of the thyroid was increased significantly (7/20 [35%]; $p < 0.01$) in rats receiving treatment for 104 weeks. The authors concluded that the minimum induction time for renal adenoma development was 26 weeks.

4.4.3. Genotoxicity

Limited information is available on the effects of bromate in bacterial or in vitromammalian systems. However, several studies have evaluated the genotoxicity of bromate in in vivosystems following both oral exposure and intraperitoneal injection.

Ishidate et al. (1984) tested the mutagenicity of 242 food additives, including potassium bromate. The result of a *Salmonella typhimurium* mutagenicity test using S9 activated strain TA100 was positive. The result of a chromosomal aberration assay (Chinese hamster fibroblasts) using potassium bromate indicated a dose-related increase in the frequency of exchange-type aberrations (including gaps).

Fujie et al. (1988) examined the acute cytogenetic effects of potassium bromate on rat bone marrow cells. Dose-dependent and time-dependent increases in the number of aberrant metaphase cells were observed in all treated animals. A statistically significant increase in aberrant cells was seen in rats receiving 3 mmol $KBrO_3$/kg (385 mg BrO_3^-/kg). The percentage of aberrant metaphase cells reached a maximum of 10.8% 18 hours after potassium bromate ingestion, followed by a decline to 0.86% at 24 hours.

Hayashi et al. (1988) used the micronucleus test to study the genotoxic potential of potassium bromate in mice. Eight-week-old mice were given either single intraperitoneal (i.p.) injections or two oral doses of 0, 25, 50, 100, 200, or 400 mg $KBrO_3$/kg (doses equivalent to 0, 19, 39, 77, 154, and 308 mg BrO_3^-/kg, respectively). Examination of femoral bone marrow cells revealed a significant increase in micronuclei at all levels of i.p. potassium bromate administration ($p < 0.01$). Oral administration of potassium bromate resulted in significantly increased micronuclei at doses of 100 mg $KBrO_3$/kg and greater.

Hayashi et al. (1989) used the micronucleus test to evaluate the genotoxic potential of potassium bromate in two strains of mice (male MS/Ae or CD-1 mice, 4/group). Gavage administration of the $KBrO_3$ increased the frequency of micronucleated polychromatic erythrocytes (MNPCEs) in a dose-responsive fashion in both strains of mice.

Nakajima et al. (1989) examined the effect of potassium bromate on the formation of MNPCEs in mice. Male mice (7-week-old MS/Ae and CD-1) were given single oral doses of 37.5, 75, 150, and 300 mg $KBrO_3$/kg by gavage (equivalent to 28.9 57.8, 115.5, and 231 mg BrO_3^-/kg, respectively). Twenty-four hours after treatment, dose-related increases in MNPCEs

were induced in both strains of treated mice. At the highest dose, the incidence of MNPCEs was 2.28%.

Awogi et al. (1992) examined the induction of micronucleated reticulocytes in CD-1 mice administered potassium bromate by intraperitoneal injection. The incidence of micronucleus formation was examined in reticulocytes from peripheral blood at 0, 24, 48, 72, or 96 hours following i.p. injection. Dose-related increases in the incidence of micronuclei of approximately 23–25-fold were observed. The incidence of micronuclei peaked by 48 hours and was still significantly increased ($p < 0.01$) compared with control levels at 72 hours. By 96 hours there were no observed differences between treated animals and controls.

Sai et al. (1992a) examined the incidence of peripheral blood cell micronuclei in male F344 rats (3/group) after i.p. administration. Micronuclei in reticulocytes (frequency, 0.9%; range 0.6%–1.2%) peaked at 32 hours and were significantly elevated ($p < 0.01$) in rats administered 46 mg BrO_3^-/kg.

Speit et al. (1999) evaluated the genotoxic potential of potassium bromate in a variety of tests with V79 Chinese hamster cells, including cytotoxicity, micronucleus, chromosome aberration, HPRT gene mutation, and comet assays. In addition, analysis was conducted on the HPRT mutations and for 8-oxodeoxyguanosine. Bromate was cytotoxic, increased the frequency of cells with micronuclei, increased the number of chromosome aberrations, and increased DNA migration in the alkaline comet assay. The majority of chromosome aberrations observed were chromatid breaks and chromatid exchanges. High-pressure liquid chromatography analysis revealed significantly increased levels of 8-oxodeoxyguanosine after potassium bromate treatment. Furthermore, potassium bromate clearly induced gene mutations at the HPRT locus. Molecular analysis of potassium bromate-induced mutations indicated a high proportion of deletion mutations. Three out of four point mutations were G-to-T transversions, which typically arise after replication of 8-oxoguanine. These results are consistent with oxidative damage induced by bromine radicals.

4.4.4. Mechanistic Studies

Several studies have examined the mechanisms by which bromate causes renal toxicity. One proposed mechanism is that exposure to bromate causes the formation of reactive intermediates, which in turn cause lipid peroxidation (LPO) and DNA damage in the kidney, but not other organs. Kidney toxicity and DNA damage following bromate exposure can be reduced

by cotreatment with antioxidants. In addition, one study identified the protein α_{2u}-globulin in the kidney of male rats treated with bromate. Although α_{2u}-globulin does not appear to be the primary mechanism by which bromate acts, it has been hypothesized that it contributes to the apparent sensitivity of male rats to the kidney effects of bromate. Finally, no mechanisms have been proposed for the development of mesotheliomas and thyroid follicular cell tumors that are consistently observed in rats after bromate exposure.

Kasai et al. (1987) studied the in vivo formation of 8-hydroxydeoxyguanosine (8-OH-dG) in liver and kidney DNA in response to the administration of potassium bromate. The formation of 8-OH-dG in tissue is indicative of damaged DNA. Five-week-old male F344 rats were given single intragastric doses of 400 mg $KBrO_3$/kg before removal of the kidneys and liver 0, 3, 6, 23, 34, or 48 hours after treatment. Tissue DNA was isolated, and the 8-OH-dG was identified by high-pressure liquid chromatography. Levels of 8-OH-dG in the liver of experimental animals were not significantly increased, and 8-OH-dG levels in the liver in control animals given known noncarcinogens were also not significantly increased. In the kidney, however, 8-OH-dG in the DNA increased up to 6 residues/10^5 8-OH-dG 24 hours after administration of $KBrO_3$. After 48 hours, a significant reduction of 8-OH-dG was observed, which the authors stated was indicative of the presence of repair enzymes in the rat kidney.

Similar results were obtained by Cho et al. (1993), who found that potassium bromate induced higher 8-OH-dG levels in the kidney (13.8 residues/10^4 dG) than in the liver (4.2 residues/10^4 dG). The 8-OH-dG levels peaked between 24 and 27 hours after i.p. injection of 500 mg $KBrO_3$/kg in Sprague-Dawley rats. By 48 hours after treatment, 8-OH-dG levels in the kidney decreased to 5.2 residues/10^4 8-OH-dG.

The enzyme that repairs 8-OH-dG is 8-hydroxydeoxyguanosine glycosylase. Lee et al. (1996) found that this enzyme is induced in a dose-dependent manner in the kidney, but not in the liver, by i.p. administration of up to 160 mg $KBrO_3$/kg potassium bromate to Fischer rats. Enzyme activity peaked by 6 hours following injection and had reached control levels by 12 hours following injection.

Sai et al. (1991) examined the renal tissue levels of 8-OH-dG, GSH, and LPO following i.p. and oral administration of bromate. In male F344 rats examined at 24, 48, 72, and 96 hours after a single i.p. administration of 70 mg $KBrO_3$/kg (53.9 mg BrO_3^-/kg), levels of 8-OH-dG, LPO, and GSH were significantly increased ($p < 0.01$) compared with control animal values. In orally treated rats (0, 20, 40, and 80 mg $KBrO_3$/kg [0, 15.4, 30.8, and 61.6 mg BrO_3^-/kg,

respectively]), levels of 8-OH-dG, GSH, and LPO were examined 48 hours postdosing. 8-OH-dG and LPO levels were significantly increased in renal tissue from the 30.8 and 61.6 mg BrO_3^-/kg dose groups. The 8-OH-dG adduct levels were elevated 2.2-fold (30.8 mg/kg) and 7.7-fold (61.6 mg/kg) compared with controls. The LPO level was more than three times that of the control animal levels. GSH levels were significantly elevated ($p < 0.01$) at a dose of 61.6 mg BrO_3^-/kg by 44% compared with control values. The authors suggested a possible mechanism for potassium bromate-induced DNA oxidation based on the increase in LPO activity and 8-OH-dG levels. Potassium bromate may produce active oxygen either directly or indirectly via reactions with intracellular molecules. The active oxygen would induce the initiation of LPO associated with the nuclear membrane followed by amplification of lipid peroxide and intermediate radicals by chain reaction. Induced LPO activity at the nuclear membrane would be in close proximity to nuclear DNA. The reaction products, in turn, would oxidize nuclear DNA. The observed increase in GSH levels may indicate a compensatory renal tissue mechanism against the production of oxidative reactants by potassium bromate.

Sai et al. (1992a) studied the suppression of potassium bromate-induced micronuclei formation in peripheral reticulocytes by antioxidants. Co-administration of sulfhydryl compounds (GSH or cysteine), but not superoxide dismutase, decreased the number of potassium bromate-induced micronuclei, suggesting that active oxygen species are involved in the clastogenic effects of potassium bromate.

Sai et al. (1992b) postulated that one mechanism for bromate toxicity included the formation of organ-specific active oxygen species. This concept was supported by evidence of singlet oxygen production resulting from the addition of potassium bromate to kidney (renal cortex cells derived from proximal tubules), but not liver, homogenates. The singlet oxygen scavengers—histidine and sodium azide—inhibited the formation of active oxygen products, whereas the superoxide radical and hydrogen peroxide scavengers—superoxide dismutase, catalase, dimethyl sulfoxide, and ethanol—produced no effect. The contrasting activity of the renal and liver homogenates in the production of singlet oxygen products supports the specificity of potassium bromate for renal cell damage (carcinomas) but not hepatic cell damage.

Sai et al. (1992c) examined the effect of GSH, cysteine, and vitamin C on potassium bromate-induced DNA and renal damage. Intraperitoneal administration of 80 mg $KBrO_3$/kg (61.6 mg BrO_3^-/kg) to 5-week-old F344 rats resulted in a 40% increase in relative kidney weight, a threefold increase in LPO and an associated threefold increase in 8-OH-dG levels. Pretreatment with sulfhydryl reducing agents (i.e., GSH and cysteine) that react with active

oxygen species inhibited the increase in these end points. Diethyl maleate, a tissue depletor of GSH, augmented the indices of potassium bromate-induced renal damage. These results suggest that the DNA and renal damage are associated with the production of active oxygen species.

Sai et. al. (1994) investigated the role of oxidative damage in potassium bromate-induced carcinogenesis in the renal proximal tubules (RPTs) and nuclear fractions. RPTs were isolated from male F344 rats and incubated with $KBrO_3$ (0–10 mM) for 8 hours in 95% air/5% CO_2. Renal nuclear fractions were isolated via centrifugation from kidney homogenates and resuspended in $KBrO_3$ (10 mM) for 2 hours at 37°C. DNA and 8-OH-dG were isolated from nuclear fractions of RPT and analyzed. The release of lactate dehydrogenase from RPT was also determined. At 0.5, 2, and 5 mM $KBrO_3$, a significant increase in the release of lactate dehydrogenase and a significant decrease in protein-SH content in RPT (75%, 68%, and 43%, respectively, of control values) was seen in a time- and concentration-dependent manner. 8-OH-dG levels in RPT and the ratio of 15-peroxidized arachidonic acid to the total isomers (17-, 18-, and 19-peroxidized arachidonic acid), an indicator of LPO, were also increased at 2 and 5 mM $KBrO_3$. 8-OH-dG levels in renal nuclei were also increased approximately 2-fold following incubation with autooxidized methyl linolenate, a lipid-peroxidizing system. The authors suggested that the potassium bromate-induced carcinogenesis may be due to LPO and the subsequent DNA damage sustained in RPT, the target site for renal carcinogenesis.

Because earlier toxicity studies had demonstrated the presence of hyaline droplets in male rat kidney following bromate exposure, the role of cell proliferation in bromate-induced carcinogenesis was evaluated (Umemura et al., 1993). Hyaline droplets were observed in the kidney tubules of male, but not female, F344 rats treated with 500 ppm $KBrO_3$ or $NaBrO_3$ in drinking water for 2 weeks. Hyaline droplets were not observed in male rats treated with 1,750 ppm $KBrO_3$. Immunohistochemical staining revealed that the droplets contained α_{2u}-globulin. In addition, cell proliferation was increased in male, but not female, rats treated with potassium or sodium bromate for up to 8 weeks.

In another study, Umemura et al. (1995) investigated the role of oxidative stress and cell proliferation in potassium bromate-induced carcinogenesis in female F344 rats, which do not accumulate α_{2u}-globulin in their kidneys. Unlike liver, renal 8-OH-dG levels were significantly increased compared with controls. Likewise, cell proliferation in the proximal convoluted tubular cells was significantly increased compared with controls but was unchanged in the liver. A significantly higher number of atypical tubules, atypical hyperplasia, and renal cell tumors was seen in animals treated with potassium bromate. However, no significant effect was observed on

liver tumorigenesis. The authors concluded that oxidative stress is associated with tumor promotion in female rats. However, in male rats, oxidative mechanisms could be cooperating with α_{2u}-globulin-mediated cell proliferation to account for the sex differences observed in bromate kidney toxicity.

Ballmaier and Epe (1995) observed that in cell-free systems or in in vitromammalian cell cultures the reduction of potassium bromate by GSH actually generates a short-lived reactive intermediate that induces 8-hydroxyguanine. The damaged DNA was not associated with cytotoxicity in the cell cultures. The results obtained by these authors are in contrast to earlier in vivo studies in which potassium bromate and GSH were administered together. The authors concluded that these differences are due to the fact that, in vivo, reduction of potassium bromate to inactive bromide occurs before bromate reaches the target tissue. The reactive intermediate responsible for the DNA damage is thought to be the bromine radical or bromine oxides, consistent with a finding that molecular bromine gives rise to the same DNA damage profile as potassium bromate.

In a recent study, Chipman et al. (1998) proposed a dual role for GSH in the genotoxicity of potassium bromate. Consistent with the findings of Ballmaier and Epe (1995), these authors found that incubation of isolated calf thymus with both potassium bromate and GSH produced 8-OH-dG, whereas incubation with potassium bromate alone did not produce any DNA damage. These data suggest a direct, activating role for GSH in vitro. However, data from in vivo systems suggest that GSH has a protective effect. Chipman et al. (1998) found that 8-OH-dG was not elevated in either total DNA or mitochondrial DNA from rat kidney perfused in situ with 5 mM $KBrO_3$ for up to 1 hour. A single i.p. dose of 100 mg $KBrO_3$/kg caused a significant increase in lipid peroxides, 8-OH-dG, and oxidized GSH. Pretreatment with diethyl maleate to deplete GSH enhanced the toxicity of potassium bromate. In contrast, a single i.p. dose of 20 mg $KBrO_3$/kg had no effect on either toxicity or oxidative stress. The authors concluded that this study contributes to the evidence that a threshold exists for potassium bromate's effects on DNA and that a nonlinear dose-response relationship exists in renal carcinogenesis.

In Syrian hamster embryo cells in vitro, potassium bromate was found to increase gap junctional intercellular communications at concentrations greater than or equal to 10,000 µM (Mikalsen and Sanner, 1994).

Kutom et al. (1990) postulated that the gastrointestinal irritation may be due to conversion of bromate to hypobromous acid in the stomach. The characteristic renal injury is

suspected to be due to the oxidizing potential of bromate (Mack 1988), and this is supported by the finding of acute renal lipid peroxidation in rats given potassium bromate (Kurokawa et al 1987).

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS

Although no long-term or epidemiological studies in humans are available, case studies of acute exposure in both children and adults indicate that early symptoms of bromate poisoning include gastrointestinal and CNS effects. Kidney failure and hearing loss follow initial symptoms after several hours; hearing loss appears to be irreversible. Although the ototoxicity observed in humans following acute exposure was not observed in rats and mice, it is not known whether the studies adequately evaluated this endpoint. Several subchronic or chronic studies in rats and mice indicate that the kidney is the primary target organ following long-term oral exposure to bromate. After rats received a 13-week exposure to doses of 63 mg BrO_3^-/kg-day (Kurokawa et al., 1990), the following nonneoplastic effects were observed: inhibition of body weight gain; significant increases in several serum parameters, including BUN; and droplets of various sizes and regenerative changes in the renal tubules. Similar effects were observed in chronic studies of oral bromate exposure (Nakano et al., 1989; Kurokawa et al., 1986b; DeAngelo et al., 1998). The following nonneoplastic effects have been reported following long-term exposure: increased BUN; increased severity of nephropathic changes; degenerative and necrotic kidney lesions, including hyaline casts in the tubular lumen, hyaline droplets, eosinophilic bodies, and brown pigments in the tubular epithelium; and urothelial hyperplasia of the transitional epithelium of the renal pelvis. No nonneoplastic effects have been reported in tissues other than the kidney.

Short-term studies in both humans and animals provide supporting evidence that the kidney is the primary target organ following bromate exposure. In the majority of cases of acute bromate exposure in humans, renal failure develops within several hours to days. The amount of time required to recovery of renal function varied from 7 days to 5 weeks, and in two cases, renal function was never restored. Histological examination of renal biopsies indicated interstitial edema, interstitial fibrosis, tubular atrophy, epithelial separation of the proximal tubules, disrupted basement membranes, casts in proximal tubules, and tubular cell regeneration. Glomeruli were not affected. The kidney effects of acute oral exposure in animals parallels those observed in humans. Kidney pathology observed in animals includes epithelial dilation of tubules; necrosis, degenerative, and regenerative changes in the proximal tubules; and accumulation of eosinophilic droplets in the proximal tubules.

Available evidence suggests that one mechanism of kidney toxicity is oxidative damage and lipid peroxide formation. Treatment with potassium bromate has been demonstrated to result in increased lipid peroxide formation in kidney, increased relative kidney weight, and increased serum levels of BUN and creatinine (Sai et al., 1992c; Kurokawa et al., 1990). Concurrent treatment with potassium bromate and GSH reduces mortality (Kurokawa et al., 1990) and prevents the increase in LPO, kidney weight, BUN, and creatinine associated with bromate treatment alone (Kurokawa et al., 1990; Sai et al., 1992c). Conversely, concurrent treatment with potassium bromate and diethyl maleate, which depletes GSH, enhances mortality and toxicity associated with bromate treatment alone (Kurokawa et al., 1990; Sai et al., 1992c). Hyaline droplets have been observed in renal tubules of rats following bromate exposure (Kurokawa et al., 1986b, 1990), which led investigators to evaluate the potential role of α_{2u}-globulin in kidney toxicity. Umemura et al. (1993) demonstrated that α_{2u}-globulin is present in the hyaline droplets observed in male rat renal tubules following bromate exposure. Therefore, α_{2u}-globulin may contribute to the kidney toxicity observed in male rats. However, because bromate induces nonneoplastic kidney lesions (Kurokawa et al., 1986b), oxidative damage (Umemura et al., 1995), and cell proliferation (Umemura et al., 1995) in female rats, which do not accumulate α_{2u}-globulin, accumulation of α_{2u}-globulin is not likely to be the primary mechanism of bromate toxicity. Rather, α_{2u}-globulin may contribute to the apparent increased sensitivity of male rats to the kidney effects of bromate.

No data regarding the noncancer effects of bromate following inhalation are available in humans or animals. Therefore, a hazard characterization for the inhalation route is precluded.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

Three key studies (Kurokawa et al., 1986a, 1986b; DeAngelo et al., 1998) demonstrated the carcinogenicity of bromate in animals. All studies were well conducted using an appropriate route of exposure and adequate numbers of animals. In the studies, the MTD was reached, as evidenced by effects on survival and body weight in the high-dose groups. There is some concern that the high dose in each of these studies (28.7 mg BrO_3^-/kg-day, DeAngelo et al., 1998; 19.6 mg BrO_3^-/kg-day, Kurokawa et al., 1986b; 33 mg BrO_3^-/kg-day, Kurokawa et al., 1986a) exceeded the MTD for male rats. However, in all three studies, the decrease in survival began to appear relatively late in the study: approximately week 70 in the Kurokawa et al. (1986a, 1986b) studies and approximately week 79 in the DeAngelo et al. (1998) study. Two studies reported the time of first tumor observation: In Kurokawa et al. (1986b), the first tumor of any type was observed at 14 weeks, and in DeAngelo et al. (1998), the first tumor of any type

was observed at 26 weeks. Therefore, the male rats in these studies survived long enough to have developed tumors. In addition, in the DeAngelo et al. (1998) study, the decreased survival and body weight gain appeared to be caused by the heavy mesothelioma burden of the animals (Wolf, 1998a); the cause of decreased survival and body weight gain in the Kurokawa et al. (1986b) study is not apparent. The decreased survival in the high-dose groups in these studies does not compromise these studies for use in risk assessment.

Several aspects of these bioassay studies support the conclusion that bromate has the potential to be a carcinogen. From the evidence in rats, relevance to humans is assumed. First, tumors were observed at multiple sites, including the kidney (adenomas and carcinomas), the thyroid (follicular cell adenomas and carcinomas), and the peritoneum (mesotheliomas). In DeAngelo et al. (1998), the mesotheliomas arose from the *tunica vaginalis* testis and spread throughout the peritoneal cavity on the serosal surfaces of many organs. Kurokawa et al. (1986a, 1986b) do not specify the origin of the peritoneal mesotheliomas observed. Male rats had tumors at all three sites, whereas female rats had only kidney tumors. However, the kidney tumors in female rats developed in the absence of the significant effects on survival and body weight observed in the male rats. The development of tumors at multiple sites supports the human cancer potential of bromate, because the more tumor sites are observed, the more likely that some of the mechanisms will be relevant to humans.

Second, a clear dose-response relationship exists in tumor incidence and in severity/progression of tumors. Kurokawa et al. (1986a) observed statistically significantly increased incidence of renal dysplastic foci, a preneoplastic lesion, at doses of 1.3 mg BrO_3^-/kg-day and greater; statistically significantly increased incidence of renal adenomas at doses of 5.6 mg BrO_3^-/kg-day and greater; and increased incidence of renal carcinoma at the high dose of 33 mg BrO_3^-/kg-day in male rats. Kurokawa et al. (1986b) observed dose-response relationships for kidney tumors in both male and female rats. Kurokawa et al. (1986a) observed dose-response relationships for two other tumor types, mesotheliomas and thyroid follicular cell, in male rats. DeAngelo et al. (1998) observed dose-response relationships for all three tumor types in rats.

The evidence is too limited to give high confidence in a conclusion about any mode of carcinogenic action. The genotoxicity of bromate has been evaluated in a variety of in vitro and in vivosystems, with consistently positive results. Bromate has tested positive in the *Salmonella typhimurium* assay in the presence of metabolic activation and in an in vitrotest for chromosomal aberrations, using Chinese hamster fibroblasts (Ishidate et al., 1984). Dose-dependent increases

in the number of aberrant metaphase cells were observed following single oral doses of potassium bromate to Long-Evans rats (Fujie et al., 1988). Bromate caused significant increases in the number of micronuclei following either i.p. injection (Hayashi et al., 1988; Awogi et al., 1992) or gavage dose (Hayashi et al., 1989; Nakajima et al., 1989) in mice. Also, i.p. injection of bromate in F344 rats resulted in significantly increased micronuclei in reticulocytes (Sai et al., 1992a). However, bromate has not been tested for gene mutation in mammalian cells.

Oxidative stress may play a role in the formation of kidney tumors; treatment with bromate causes an increase of 8-OH-dG in the kidney (both total DNA and mitochondrial DNA) but not in other organs (Ballmaier and Epe, 1995; Chipman et al., 1998; Sai et al., 1991, 1992a, 1992b, 1992c, 1994; Kurokawa et al., 1990). Formation of 8-OH-dG has been demonstrated to induce G-T transversions and to contribute to the activation of oncogenes and/or inactivation of suppressor genes (Sai et al., 1994). Two mechanisms of bromate-mediated DNA damage have been proposed: direct interaction with DNA following GSH activation, and indirect damage via lipid peroxides (Ballmaier and Epe, 1995; Chipman et al., 1998). Recent studies suggest that in the intact kidney, there is not a direct mechanism of DNA damage; rather, at toxic doses, bromate induces DNA damage through LPO (Chipman et al., 1998). However, the overall evidence is insufficient to establish LPO and free-radical production as the key events responsible for the induction of kidney tumors. In addition, no data are currently available to suggest that any single mechanism, including oxidative stress, is responsible for the production of thyroid and peritoneal tumors by bromate.

Some evidence suggests that cell proliferation plays a role in enhancing renal carcinogenesis by bromate. Umemura et al. (1993) demonstrated that α_{2u}-globulin is present in the hyaline droplets observed in male rat renal tubules following bromate exposure. Later studies in female rats demonstrated that bromate induces cell proliferation in renal tubules independent of α_{2u}-globulin (Umemura et al., 1995). The demonstration of kidney tumors in female rats and mesotheliomas and thyroid tumors in male rats suggests that α_{2u}-globulin is not the primary mechanism of bromate carcinogenicity, although it may contribute to the apparent sensitivity of male rats to the kidney effects of bromate. Therefore, bromate carcinogenesis is potentially relevant to humans. More data are needed to clarify the role of cell proliferation in bromate carcinogenesis.

Observation of tumors at relatively early time points and the positive response of bromate in a variety of genotoxicity assays suggest that the predominant mode of action at low doses is DNA reactivity. Although there is limited evidence to suggest that the DNA reactivity in kidney

tumors may have a nonlinear dose-response relationship, there is no evidence to suggest that this same dose-response relationship operates in the development of mesotheliomas or thyroid tumors. Therefore, in the absence of a biologically based model, the assumption of low-dose linearity is considered to be a reasonable public health protective approach at this time for estimating the potential risk for bromate.

The International Agency for Research on Cancer (IARC, 1986) has classified potassium bromate as a Group 2B carcinogen, possibly carcinogenic to humans. IARC concluded that no data existed on the carcinogenicity of potassium bromate in humans but that sufficient evidence of carcinogenicity in experimental animals was available. Specifically, IARC noted the observation of renal cell tumors in both sexes of rats, peritoneal mesotheliomas in male rats, and thyroid tumors in female rats following administration of potassium bromate in drinking water. In addition, IARC noted sufficient evidence of genetic activity in short-term tests, including mutation in prokaryote as well as chromosome effects in mammalian cells both in vivo and in vitro.

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), bromate would be classified as Group B2, probable human carcinogen, on the basis of no evidence in humans and adequate evidence of carcinogenicity in male and female rats.

Under the *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996), bromate should be evaluated as a *likely* human carcinogen by the oral route of exposure. Insufficient data are available to evaluate the human carcinogenic potential of bromate by the inhalation route. Although no epidemiological studies or studies of long-term human exposure to bromate are available, bromate is carcinogenic to male and female rats following exposure in drinking water. Given the limited data on possible mechanisms of carcinogenic action for bromate, it is a reasonable assumption that the production of tumors in rats occurs by a mode of action that is relevant to humans. With the lack of human data and the uncertainty surrounding the mode of action, the human relevance of the rat data relies on the assumption that the rat data are relevant to humans.

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

Limited data exist on which to make an assessment of possible childhood susceptibility. Case reports on the effect of accidental or suicidal ingestion of bromate suggest that children and adults demonstrate similar symptoms following ingestion of similar doses. No data are available regarding age-related differences in absorption, distribution, metabolism, or excretion of bromate. Limited evidence suggests that bromate may be a male reproductive toxicant, but at a higher dose than that which results in kidney toxicity. No data are available that describe the effects of in uteri or neonatal exposure to bromate.

4.7.2. Possible Gender Differences

The extent to which men and women differ in susceptibility to bromate is not known. No human studies have described gender differences. In Kurokawa et al. (1986b), limited evidence was presented that male rats are more sensitive to bromate than female rats are. In male rats, but not female rats, significant decreases in survival and body weight were observed. In addition, the earliest tumor was observed at week 14 in male rats, but at week 85 for female rats. At least one study (Umemura et al., 1993) has suggested that α_{2u}-globulin contributes to the renal toxicity observed in male rats. α_{2u}-Globulin is a protein unique to male rats and may contribute to the sensitivity of male rats to bromate. Because humans do not have α_{2u}-globulin, it is not likely that human males will exhibit the same sensitivity as male rats.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE

5.1.1. Choice of Principal Study and Critical Effect—With Rationale and Justification

One subchronic study (Kurokawa et al., 1990) and several chronic studies (Nakano et al., 1989; Kurokawa et al., 1986a,b; DeAngelo et al., 1998) have demonstrated noncancer effects in the kidney following oral exposure to bromate. However, only DeAngelo et al. (1998) sufficiently characterized the dose-response relationship of the noncancer effects to identify a NOAEL and LOAEL.

In a 13-week study, Kurokawa et al. (1990) demonstrated degenerative changes in renal tubules at doses of 63 mg BrO_3/kg-day and greater. However, the study incompletely reports noncancer effects, and there is insufficient information available from the study to determine whether the next lower dose, 32 mg BrO_3^-/kg-day, is an adverse effect level. In Nakano et al. (1989), the only dose tested, 30 mg BrO_3^-/kg-day, caused karyopyknotic foci in renal tubules and degenerative changes in the renal cortex. However, DeAngelo et al. (1998) have identified a lower NOAEL and LOAEL than these studies.

The only reproductive/developmental study (Wolf and Kaiser, 1996) suggests that bromate may be a male reproductive toxicant, causing a decrease in epididymal sperm density. This study identified a LOAEL for male reproductive effects of 22 mg BrO_3^-/kg-day and a NOAEL of 7.7 mg BrO_3^-/kg-day. However, the DeAngelo study suggests that kidney toxicity is the critical effect, because kidney damage was observed at lower doses than were reproductive effects.

DeAngelo et al. (1998) observed statistically significant increases in relative liver weight, absolute and relative kidney weight, absolute and relative thyroid weight, and relative spleen weight in rats in the 28.7 mg/kg-day dose group. Nonneoplastic kidney lesions observed in rats included a significant dose-dependent increase in the incidence of urothelial hyperplasia at doses of 6.1 mg/kg-day and foci of mineralization of the renal papilla and eosinophilic droplets in the proximal tubule epithelium. No other treatment-related nonneoplastic effects were observed in any other tissue examined. Based on urothelial hyperplasia in male rats, this study identifies a NOAEL of 1.1 mg BrO_3^-/kg-day and a LOAEL of 6.1 mg BrO_3^-/kg-day.

5.1.2. Method of Analysis—NOAEL/LOAEL

A NOAEL/LOAEL approach was used to derive the RfD for bromate. The RfD was based on the NOAEL of 1.1 mg BrO_3^-/kg-day identified in DeAngelo et al. (1998). The authors reported that doses of potassium bromate were calculated from measured body weights and mean daily water consumption. The doses of bromate ion were obtained by adjusting the authors' reported doses by the ratio of bromate molecular weight to potassium bromate molecular weight.

5.1.3. RfD Derivation, Including Application of Uncertainty Factors and Modifying Factors

An uncertainty factor (UF) of 10 is applied to account for extrapolating from animals to humans, and a factor of 10 is used to protect sensitive subpopulations and to account for potential differences between adults and children. A factor of 3 is used to account for some deficiencies in the database. The bromate database consists of chronic and subchronic studies in rats and mice and a screening-level reproductive/developmental study in rats. The database is missing developmental toxicity in two species and a multigenerational study. This results in a total UF of 300.

No modifying factors are proposed for this assessment.

The RfD for bromate is as follows: RfD = 1.1 mg/kg-day ÷ 300 = 0.004 mg/kg-day (or 4E-3 mg/kg-day).

5.2. INHALATION REFERENCE CONCENTRATION

The lack of data by the inhalation route of exposure precludes the development of an inhalation reference concentration.

5.3. CANCER ASSESSMENT

5.3.1. Choice of Critical Study: Rationale and Justification

The rodent bioassay studies (Kurokawa et al., 1986a, 1986b; DeAngelo et al., 1998) clearly indicate that bromate induces tumors at multiple sites in rats. However, the tumor incidences among the three studies are different, and the nature of the dose-response is not well defined. Kurokawa et al. (1986b) observed higher incidences of both kidney tumors and peritoneal mesotheliomas in both dose groups than did Kurokawa et al. (1986a) and DeAngelo et al. (1998). However, Kurokawa et al. (1986b) did not observe the statistically significant increase in thyroid tumors that was observed in the other two studies. The tumor incidences at all three sites were similar for both Kurokawa et al. (1986a) and DeAngelo et al. (1998); however, the statistical significance of the tumor incidence varied between the studies. DeAngelo et al. (1998) observed a statistically significant increase of mesothelioma at the 6.1 mg BrO_3^-/kg-day and greater doses, a statistically significant increase of thyroid tumors at the 12.9 mg BrO_3^-/kg-day

and greater doses, and a statistically significant increase of kidney tumors only at the highest dose. Conversely, Kurokawa et al. (1986a) observed a statistically significant increase in mesotheliomas and thyroid tumors only at the highest dose tested, but they observed a statistically significant increase of kidney tumors at the 5.6 mg BrO_3^-/kg-day and greater doses. Because the DeAngelo et al. (1998) study used lower doses than the Kurokawa et al. (1986b) study and used more animals per group than the Kurokawa et al. (1986a) bioassay, DeAngelo et al. (1998) was chosen as the preferred data set for quantifying bromate cancer risk.

The strengths of DeAngelo et al. (1998) include dose-dependent results at tumor sites consistent with the Kurokawa et al. studies, adequate numbers of animals, and lower doses than Kurokawa et al. (1986b). The data are considered adequate for dose-response modeling; moreover, the availability of the individual animal data makes it possible to account for early mortality and include the interim kill results. Although DeAngelo et al. (1998) evaluated only male rats, the Kurokawa et al. (1986b) study found no difference in the response of male and female rats to development of kidney tumors. Therefore, it is reasonable to use male rat data and assume that it is valid for females. There is some concern that decreased survival in the two highest dose groups compromised the quality of the study. As discussed in section 2.4, the excessive tumor burden appears to be the cause of early mortality and decreased body weight gain in this study (Wolf, 1998a). Thyroid tumors were first seen at week 26, and kidney tumors and testicular mesotheliomas were first seen at week 52. Survival was comparable to controls until approximately week 79. Therefore, the rats survived well past the time of first tumor observation and the study is not compromised for quantifying cancer risk. Use of the Weibull time-to-tumor model should account for any effects that early mortality may have had on tumor response.

5.3.2. Dose-Response Data

Oral cancer risk was calculated on the basis of the incidence of renal tubular tumors, thyroid follicular tumors, and mesotheliomas from the DeAngelo et al. (1998) study. The analyses were conducted using the individual male rat data, including the 12-, 26-, 52-, and 77-week interim kill data, for each site demonstrating an increased cancer incidence. Benign and malignant tumors were combined for the sites (i.e., testicular mesotheliomas, kidney tubular adenomas and carcinomas, and thyroid follicular adenomas and carcinomas). The administered doses, human equivalent doses, and tumor incidences are presented in Table 5. Tumors were modeled for each tumor site separately, and then the individual tumor site risks were combined to represent the total cancer risk.

Table 5. Dose-response data

Administered dose	0 mg BrO_3^- /kg-day	1.1 mg BrO_3^- /kg-day	6.1 mg BrO_3^- /kg-day	12.9 mg BrO_3^- /kg-day	28.7 mg BrO_3^- /kg-day
Human equivalent dose	**0 mg BrO_3^- /kg-day**	**0.30 mg BrO_3^- /kg-day**	**1.7 mg BrO_3^- /kg-day**	**3.5 mg BrO_3^- /kg-day**	**7.9 mg BrO_3^- /kg-day**
Mesotheliomas					
Week 12	0/6	0/6	0/6	0/6	0/6
Week 26	0/6	0/6	0/6	0/6	0/6
Week 52	0/6	0/6	0/6	1/6	0/6
Week 77	0/6	0/6	0/6	0/6	4/6
Week 100	0/47	4/49	5/49	10/47	27/43
Kidney tubular adenomas and carcinomas					
Week 12	0/6	0/6	0/6	0/6	0/6
Week 26	0/6	0/6	0/6	0/6	0/6
Week 52	0/6	0/6	0/6	0/6	2/6
Week 77	0/6	0/6	0/6	0/5	4/6
Week 100	1/45	1/43	6/47	3/39	12/32
Thyroid follicular adenomas and carcinomas					
Week 12	0/6	0/6	0/6	0/6	0/6
Week 26	0/6	0/6	1/6	1/6	0/6
Week 52	0/6	0/6	0/6	0/6	0/6
Week 77	0/6	0/6	0/6	0/5	3/6
Week 100	0/36	4/39	1/43	4/35	14/30

5.3.3. Dose Conversion

Oral doses were converted to human equivalent doses of bromate ion by using a surface area adjustment of body weight to the 3/4 power, so that human dose in mg/kg-day = rat dose in mg/kg-day × $(0.4/70kg)^{1/4}$, where 0.4 kg is the body weight of rats in DeAngelo et al. (1998) and 70 kg is the default human body weight.

5.3.4. Extrapolation Method

Time-to-tumor analyses of male rat data from DeAngelo et al. (1998) were done to account for early mortality in the highest dose group. The general model used for the time-to-tumor analyses was the multistage Weibull model, which has the form

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$$

where P(d,t) represents the probability of a tumor by age t (in bioassay weeks) for dose d (rat dose of bromate in mg/kg-day), and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i = 0, 1, ..., k, where k = the number of dose groups - 1. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death. The analyses were conducted using the computer software TOX-RISK Version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA), which is based on Weibull models taken from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood.

Specific n-stage Weibull models were selected for the individual tumor types on the basis of the values of the log likelihoods according to the strategy used by the National Institue for Occupational Safety and Health (NIOSH, 1991). If twice the difference in log likelihoods was less than a χ-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, then the models were considered comparable and the most parsimonious model (i.e., the lowest stage model) was selected.

In time-to-tumor analysis, tumor types are categorized as either fatal or incidental. Fatal tumors are those tumors thought to act rapidly to cause an animal to die, and incidental tumors are thought not to have caused the death of an animal, or at least not rapidly. Each of the three tumor types observed in the U.S. EPA study was considered incidental (Wolf, 1998b). Thus, t_0 was set equal to 0.

Parameter estimates for time-to-tumor analyses for each tumor type are presented in Table 6. For each tumor type, a one-stage model was the preferred model.

Table 6. Parameter estimates for one-stage Weibull time-to-tumor model

Tumor	Q_0	Q_1	Z
Testicular mesothelioma	0.0	3.94×10^{-9}	3.44
Kidney tubular adenomas and carcinomas	3.78×10^{-7}	3.26×10^{-7}	2.28
Thyroid follicular adenomas and carcinomas	3.95×10^{-5}	2.63×10^{-5}	1.28

Incremental lifetime unit extra cancer risks (upper bounds) for humans (i.e., q_1*) were estimated by TOX-RISK based on a linearized low-dose extrapolation of the Weibull time-to-tumor models for the rat tumor sites. Extra risk over the background tumor rate is defined as

$$[P(d) - P(0)] / [1 - P(0)].$$

The resulting cancer potency estimates are presented in Table 7. Note that the risk estimate based on the $0.1/LED_{10}$ linear extrapolation and that based on the q_1* are in very close agreement.

The testicular mesotheliomas yield the highest upper bound unit cancer potency estimate (q_1*), 0.54 per mg BrO_3^-/kg-day.

Although the time-to-tumor modeling described previously does help account for decreased survival times in the rats, considering the tumor sites individually does not convey the total amount of risk potentially arising from multiple sites. To get some indication of the total

Table 7. Cancer potency estimates for bromate based on male rat tumors

Tumor	ED_{10}[a] (mg/kg-day)	LED_{10}[b] (mg/kg-day)	$0.1/LED_{10}$[c] [(mg/kg-day)$^{-1}$]	MLE of cancer potency[d] [(mg/kg-day)$^{-1}$]	q_1*[e] [(mg/kg-day)$^{-1}$]
Mesothelioma	0.38	0.20	0.50	0.27	0.54
Kidney	1.3	0.59	0.17	0.08	0.18
Thyroid	2.1	1.1	0.09	0.05	0.10

[a] Estimated dose resulting in a 10% increase in cancer risk.
[b] 95% lower confidence limit on estimated dose resulting in a 10% increase in cancer risk.
[c] Unit cancer risk estimate based on drawing a straight line from the LED_{10} as described for the linear extrapolation default in U.S. EPA's 1996 *Proposed Guidelines for Carcinogen Risk Assessment.*
[d] Maximum likelihood estimate of cancer potency from Weibull time-to-tumor model, calculated at a dose of 1 ng/kg-day.
[e] 95% upper confidence limit on cancer potency.
Source: DeAngelo et al., 1998.

unit risk from multiple tumor sites, assuming the tumors at these different sites arise independently, the maximum likelihood estimates (MLEs) of the unit potency from the Weibull time-to-tumor models were summed across tumor sites, and an estimate of the 95% upper bound on the sum was calculated. The TOX-RISK software provides MLEs and 95% UCLs for extra risk at various exposure levels, allowing for the calculation of unit potency estimates at those exposure levels. In summing the MLEs across the three tumor sites, it is not assumed that these tumors are caused by a similar mechanism.

The potency estimates were summed using a Monte Carlo analysis and the software Crystal Ball Version 4.0 (Decisioneering, Denver, CO). Normal distributions were assumed for the potency estimate at a human dose of 1 ng/kg-day for each tumor site, with the distribution mean equal to the MLE of potency and the standard deviation, σ, calculated according to the formula

$$95\% \text{ UCL on risk} = \text{MLE} + 1.645\ \sigma.$$

A distribution of the sum of the potency estimates was then generated by simulating the sum of estimates picked from the distributions for each tumor site (according to probabilities prescribed by those distributions) 10,000 times. This procedure yielded a mean value for the total unit risk of 0.41 per mg BrO_3^-/kg-day continuous lifetime exposure. The 95% upper bound for the total unit risk was 0.7 per mg BrO_3^-/kg-day. In comparison, summing the q_1*s across the three tumor sites yielded 0.82 per mg BrO_3^-/kg-day.

The summation analyses were repeated for potency estimates calculated at a human dose of 0.01 mg BrO_3^-/kg-day for comparison with the estimates calculated at 1 ng BrO_3^-/kg-day (a dose range of 4 orders of magnitude). The results were nearly identical. Thus, the total unit potency estimates are effectively linear up to 0.01 mg BrO_3^-/kg-day continuous lifetime exposure. A sensitivity analysis based on the contribution to variance reported that the variability associated with the risk estimate for the testicular mesotheliomas was contributing more than 85% of the variance of the sum.

The simulation analysis revealed that the assumption of normal distributions on the risk estimates is violated because some of the simulated estimates and sums were negative. Thus, if the potency estimates were constrained to be nonnegative, the true distributions would be skewed to the right rather than symmetrical, and the 95% UCL on the sum would likely be higher than that predicted under the assumption of normal distributions, although not as high as the sum of

the upper bounds. Although the violation of the assumption of a normal distribution means that the estimate of 0.70 per mg BrO_3^-/kg-day for the 95% UCL is somewhat low, the degree of underestimation is relatively small. The true 95% UCL is less than 0.82 per mg BrO_3^-/kg-day (the sum of the q_1*s).

5.3.5. Slope Factor

In summary, based on a time-to-tumor analysis of the DeAngelo et al. (1998) for testicular mesotheliomas, kidney tubular tumors, and thyroid follicular tumors in the male F344 rat and a body weight to the 3/4 power scaling factor, the best estimate of an upper bound incremental lifetime human unit extra cancer risk is 0.70 per mg BrO_3^-/kg-day.

No inhalation slope factor could be calculated, in the absence of relevant data.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HAZARD CHARACTERIZATION

Bromate is a disinfection byproduct that is formed during the ozonation of waters containing bromide ion. No information was located regarding the concentrations of bromate in ozonated waters, but laboratory studies indicated that the degree of bromate formation depends on ozone concentration, pH, and contact time.

6.1.1. Characterization of Noncancer Hazard

No long-term human studies on the health effects of bromate are available. However, case studies of acute exposure in children and in adults indicate that early symptoms of bromate poisoning include gastrointestinal and CNS effects. Kidney failure and hearing loss follow initial symptoms after several hours; hearing loss appears to be irreversible. Although the ototoxicity observed in humans following acute exposure was not observed in rats and mice, it is not known whether the studies adequately evaluated this endpoint. Subchronic and chronic oral studies (Nakano et al., 1989; Kurokawa et al., 1986a, 1986b, 1990; DeAngelo et al., 1998) provide evidence that the kidney is the target organ of bromate toxicity. Specific effects include necrosis and degenerative changes in renal tubules and urothelial hyperplasia. Observation of similar

kidney effects in humans (Benson, 1951; Parker and Barr, 1951; Quick et al., 1975; Gradus et al., 1984; Warshaw et al., 1985; Lue et al., 1988; Mack, 1988; Lichtenberg et al., 1989; Watanabe et al., 1992) and animals following acute oral exposure provides supporting evidence that the kidney is the target organ of bromate. A screening-level reproductive/developmental study (Wolf and Kaiser, 1996) suggests that bromate may be a male reproductive toxicant, causing a decrease in epididymal sperm density. However, the reproductive effects appear to occur at higher doses than do kidney effects.

A major uncertainty of the noncancer hazard characterization is the relevance of the kidney effects to humans. Although case reports of acute bromate exposure in humans suggest that the kidney is the target organ, no long-term studies corroborate that humans will exhibit kidney toxicity following lifetime bromate exposure. Although the kidney is clearly the target organ in rats following chronic exposure, no noncancer effects of any type have been observed in mice following chronic exposure. Therefore, these species differences contribute to the uncertainty regarding extrapolation of animal data to humans. There are also species differences in the observation of ototoxicity in humans, but not animals. Nevertheless, it is a reasonable assumption that the rat data are applicable to humans. Another source of uncertainty pertains to potential subpopulations that may be sensitive to bromate exposure. For example, people with preexisting kidney conditions, such as diabetics, may be more sensitive to the effects of bromate. In addition, no data are available to indicate whether children are more susceptible to the effects of bromate than are adults. However, the limited acute data seem to indicate that children and adults have equivalent responses to bromate.

Lack of data on the toxicity of inhaled bromate precludes the characterization of the hazard posed to humans by inhalation exposure to bromate.

6.1.2. Characterization of Carcinogenicity

The major limitation of the bromate hazard characterization is the lack of data on the effects in humans of long-term exposure to bromate. The available human data are limited to case reports of toxicity following acute, accidental ingestion. Although bromate is clearly carcinogenic in male and female rats, no dose-related increases in tumor incidence have been observed in mice. Therefore, to extrapolate rat tumor data for bromate to the human situation, it must be assumed that humans will respond like rats. Nevertheless, the choice of using the rat tumor data from DeAngelo et al. (1998) in the absence of human data is a reasonable assumption.

Overall, not enough evidence exists to give high confidence in a conclusion about any mode of carcinogenic action. Studies are available showing that bromate is mutagenic in bacteria and causes chromosomal aberrations (Ishidate et al., 1984; Fujie et al., 1988; Hayashi et al., 1988; Hayashi et al., 1989; Sai et al., 1992a). The mode of action by which bromate induces mutations and, thus, tumors in target organs is uncertain. Studies are available showing that bromate may generate oxygen radicals, which increase LPO and damage DNA (Kasai et al., 1987; Sai et al., 1991; Sai et al., 1992a, 1992b, 1992c; Sai et al., 1994; Umemura et al., 1995). However, no data are available that link this proposed mechanism with tumor induction. Thus, the available evidence is insufficient to establish this mechanism as a key event in the induction of tumors at the target organs observed. In addition, bromate exposure induces α_{2u}-globulin in male rat kidney and induces cell proliferation in female rat kidney by an unidentified mechanism. Therefore, additional uncertainty exists regarding the role of these mechanisms in bromate carcinogenicity and the doses at which these mechanisms operate. Given the uncertainty about the mode of action, a science policy decision is made to use a low-dose linear extrapolation approach because it is more protective of public health. The cancer risk estimation presented for bromate is considered to be protective of susceptible groups, including children, given that the low-dose linear default approach is used as a conservative approach.

6.2. DOSE-RESPONSE CHARACTERIZATION

6.2.1. Characterization of Noncancer Assessment

A noncancer quantitative assessment of low-level chronic bromate exposure is based on animal studies; no long-term human studies on the effects of bromate are available. Kidney effects, including degenerative changes in the renal tubules and urothelial hyperplasia, appear to be the most sensitive effects. The human chronic dose of ingested bromate considered to be without deleterious noncancer effect (the RfD) is 4E-3 mg BrO_3^-/kg-day. This value is based on a NOAEL for urothelial hyperplasia identified in a chronic rat study of 1.1 BrO_3^- mg/kg-day. The RfD was calculated by dividing the NOAEL by a UF of 300.

A UF of 10 is applied to account for extrapolation from animals to humans, and a factor of 10 is used to protect sensitive subpopulations and to account for potential differences between adults and children. A factor of 3 is used to account for some deficiencies in the database.

The overall confidence in this RfD assessment is medium. Confidence in the principal study is high because the study was well conducted, used adequate numbers of animals, and

evaluated appropriate endpoints. Confidence in the database is medium. Although the database contains several subchronic and chronic studies of bromate, only one study provides adequate dose-response information regarding renal effects of bromate. A screening-level reproductive/developmental study suggests bromate may be a male reproductive toxicant; this effect needs to be more completely characterized. In addition, the database is missing a reproductive study for a second species, developmental studies for two species, and a multigeneration study. Reflecting medium confidence in the database, the confidence in the RfD is medium.

A major source of uncertainty regarding the noncancer quantitative assessment is the lack of dose-response data available in the database. Although several studies qualitatively describe the kidney effects in rats following bromate exposure (Kurokawa et al., 1986b; Kurokawa et al., 1990), only one study (DeAngelo et al., 1998) provides dose-response data to describe the kidney toxicity. Therefore, some uncertainty exists regarding the appropriateness of the NOAEL for bromate.

Currently, no data are available to derive an RfC for bromate. No data are available to predict the effect of inhaled bromate on the respiratory tract; therefore, it would not be appropriate to derive an RfC for bromate on the basis of oral data.

6.2.2. Characterization of Cancer Assessment

The hazard characterization of bromate suggests that the dose-response assessment should apply a linear extrapolation from data in the observable range to the low-dose region because of the lack of understanding of bromate's mode of action and the positive mutagenicity data. A low-dose linear extrapolation based on the U.S. EPA bromate study (DeAngelo et al., 1998) was conducted using a one-stage Weibull time-to-tumor model. This model was selected because it can account for the early mortality observed in treated animals compared with control animals. Modeling was conducted on the individual tumor types, and cancer potency estimates were generated for the individual sites and for total risk from all three sites combined. Incidence of testicular mesotheliomas was the most sensitive response; however, the total cancer potency estimate was selected because it accounts for the total cancer risk posed by tumors arising at multiple sites. It is assumed that these different tumors at different sites arise independently and that the different tumors are not necessarily induced by similar mechanisms. A source of uncertainty is the interspecies differences between rats and humans. Studies indicate that mice are less sensitive to the effects of bromate than are rats. The reasons for this difference are

unknown, and it is also unknown what the relative sensitivity between rats and humans is. Another uncertainty concerns how well the linear extrapolation predicts the low-dose human risks for bromate.

Based on low-dose linear extrapolation, using the time-to-tumor analysis, and using the Monte Carlo analysis to sum the cancer potency estimates for kidney renal tubule tumors, mesotheliomas, and thyroid follicular cell tumors, an upper bound cancer potency estimate for bromate ion is 0.70 per mg/kg-day. This potency estimate corresponds to a drinking water unit risk of 2×10^{-5} per µg/L, assuming a daily water consumption of 2 L/day for a 70-kg adult. Lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} are associated with bromate concentrations of 5, 0.5, and 0.05 µg/L, respectively.

A major source of uncertainty in these estimates is from the interspecies extrapolation of risk from rats to humans. The limited results in mice (Kurokawa et al., 1986b; DeAngelo et al., 1998) suggest that this species is less sensitive to bromate-induced carcinogenicity than is the rat. The reasons for the interspecies differences are unknown, and it is not known whether humans are more similar to rats or to mice.

Another major source of uncertainty in the unit potency estimate is the linear extrapolation of high-dose risks observed in the rat bioassay to lower doses that would be of concern from human environmental exposures. A multistage Weibull time-to-tumor model was used because it can take into account the differences in mortality between the exposure groups in the rat bioassay; however, it is unknown how well this model predicts the risks for low exposure to bromate. Although there are also uncertainties pertaining to the specific assumptions used in conducting the multistage Weibull time-to-tumor analyses and the Monte Carlo analysis for summing across the tumor sites, these are considered minor compared with the uncertainties introduced by the interspecies and high-to-low dose extrapolations.

7. REFERENCES

Awogi, T; Murata, K; Uejima, M; et al. (1992) Induction of micronucleated reticulocytes by potassium bromate and potassium chromate in CD-1 male mice. Mutat Res 278(2-3):181-185.

Ballmaier, D; Epe, B. (1995) Oxidative DNA damage induced by potassium bromate under cell-free conditions and in mammalian cells. Carcinogenesis 16:335-342.

Benson, CI. (1951) Potassium bromate poisoning. Br Med J 1:1516.

Budavari, S; O'Neil, MJ; Smith, A; et al., eds. (1989) The Merck index: an encyclopedia of chemicals, drugs and biologicals. 11th ed. Rahway, NJ: Merck and Company, Inc.

Chipman, JK; Davies, JE; Parsons, JL; et al. (1998) DNA oxidation by potassium bromate; a direct mechanism or linked to lipid peroxidation? Toxicology, in press.

Cho, DH; Hong, JT; Chin, K; et al. (1993) Organotropic formation and disappearance of 8-hydroxydeoxyguanosine in the kidney of Sprague-Dawley rats exposed to adriamycin and $KBrO_3$. Cancer Lett 74: 141-145.

DeAngelo, AB; George, MH; Kilburn, SR; et al. (1998) Carcinogenicity of potassium bromate administered in the drinking water to male B6C3F1 mice and F344/N rats. Toxicol Pathol 26(4): July/August, in press.

Fujie, K; Shimazu, H; Matsuda, M; et al. (1988) Acute cytogenetic effects of potassium bromate on rat bone marrow cells in vivo. Mutat Res 206:455–458.

Fujii, M; Oikawa, K; Saito, H; et al. (1984) Metabolism of potassium bromate in rats: I. In vivo studies. Chemosphere 13:1207-1212.

Glaze, WH. (1986) Reaction products of ozone: a review. Environ Health Perspect 69:151-157.

Gradus (Ben-Ezer), D; Rhoads, M; Bergstrom, LB; et al. (1984) Acute bromate poisoning associated with renal failure and deafness presenting as hemolytic uremic syndrome. Am J Nephrol 4:188-191.

Haag, WR; Holgne, J. (1983) Ozonation of bromide containing waters: kinetics of formation of hypobromous acid and bromate. Environ Sci Technol 17:261-267.

Hamada, F; Ohzono, S; Yamada, S; et al. (1990) A case of acute potassium bromate intoxication. Fukuoka Igaku Zasshi 81:271-276.

Hayashi, M; Sutou, S; Shimada, H; et al. (1989) Difference between intraperitoneal and oral gavage application in the micronucleus test: the 3rd collaborative study by CSGMT/JEMS-HMS. Mutat Res 223:329-344.

Hayashi, M; Kishi, M; Sofuni, T; et al. (1988) Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem Toxicol 26:487-500.

Hazardous Substance Data Bank. (HSDB) (1991) Bethesda, MD: National Library of Medicine, National Toxicology Information Program. April 1991.

International Agency for Research on Cancer. (IARC) (1986) Potassium bromate. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, volume 40. Lyon, France: World Health Organization, International Agency for Research on Cancer, 207-220.

Ishidate, M; Sofuni, T; Yoshikawa, K; et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22:623-636.

Kasai, H; Nishimura, S; Kurokawa, Y; et al. (1987) Oral administration of the renal carcinogen, potassium bromate, specifically produces 8-hydroxydeoxyguanosine in rat target organ DNA. Carcinogenesis 8:1959-1961.

Kawana, K; Nakaoka, T; Horiguchi, Y; et al. (1991) Toxicological study of potassium bromate: 2. Hepatotoxic effects of the potassium bromate and benzo[a]pyrene simultaneous administration in mice. Eisei Kagaku-Jpn J Toxicol Environ Health 37(4):266-275.

Krewski, D; Crump, KS; Farmer, J; et al. (1983) A comparison of statistical methods for low dose extrapolation utilizing time-to-tumor data. Fundam Appl Toxicol 3:140-160.

Kurata, Y; Diwan, BA; Ward, JM. (1992) Lack of renal tumour-initiating activity of a single dose of potassium bromate, a genotoxic renal carcinogen in male F344/NCr rats. Food Chem Toxicol 30(3):251-259.

Kurokawa, Y; Hayashi, Y; Maekawa, A; et al. (1983) Carcinogenicity of potassium bromate administered orally to F344 rats. J Natl Cancer Inst 71:965-972.

Kurokawa, Y; Aoki, S; Matsushima, Y; et al. (1986a) Dose-response studies on the carcinogenicity of potassium bromate in F344 rats after long-term oral administration. J Natl Cancer Inst 77:977-982.

Kurokawa, Y; Takayama, S; Konishi, Y; et al. (1986b) Long-term in vivo carcinogenicity tests of potassium bromate, sodium hypochlorite and sodium chlorite conducted in Japan. Environ Health Perspect 69:221-236.

Kurokawa, Y; Matsushima, Y; Takamura, N; et al. (1987) Relationship between the duration of treatment and the incidence of renal cell tumors in male F344 rats administered potassium bromate. Jpn J Cancer Res 78:358-364.

Kurokawa, Y; Maekawa, A; Takahashi, M; et al. (1990) Toxicity and carcinogenicity of potassium bromate--a new renal carcinogen. Environ Health Perspect 87:309-335.

Kutom, A; Bazilinski, NG; Magana, L; et al. (1990) Bromate intoxication: hairdressers' anuria. Am J Kidney Dis 15(1):84-85.

Kuwahara, T; Ikehara, Y; Kanatsu, K; et al. (1984) 2 Cases of potassium bromate poisoning requiring long-term hemodialysis therapy for irreversible tubular damage. Nephron 37:278-280.

Lee, Y-S; Choi, J-Y; Park, M-K; et al. (1996) Induction of oh^{8}Gua glycosylase in rat kidneys by potassium bromate ($KBrO^{3}$), a renal carcinogen. Mutat Res 364:227-233.

Lichtenberg, R; Zeller, WP; Gatson, R; et al. (1989) Bromate poisoning. J Pediatr 114:891-894.

Lue, JN; Johnson, CE; Edwards, DL. (1988) Bromate poisoning from ingestion of professional hair-care neutralizer. Clin Pharm 7:66-70.

Mack, RB. (1988) Round up the usual suspects. Potassium bromate poisoning. N C Med J 49:243-245.

Matsumoto, I; Morizono, T; Paparella, MM. (1980) Hearing loss following potassium bromate: two case reports. Otolaryngol Head Neck Surg 88:625-629.

Matsushima, Y; Takamura, N; Imazawa, T; et al. (1986) Lack of carcinogenicity of potassium bromate after subcutaneous injection to newborn mice and newborn rats. Sci Rep Res Inst Tohoku Univ 33:22-26.

Mikalsen, S-O; Sanner, T. (1994) Increased gap junctional intercellular communication in Syrian hamster embryo cells treated with oxidative agents. Carcinogenesis 15:381-387.

Nakajima, M; Kitazawa, M; Oba, K; et al. (1989) Effect of route of administration in the micronucleus test with potassium bromate. Mutat Res 223:399-402.

Nakano, K; Okada, S; Toyokuni, S; et al. (1989) Renal changes induced by chronic oral administration of potassium bromate or ferric nitrilotriacetate in Wistar rats. Jpn Arch Intern Med 36:41-47.

NAS (National Academy of Sciences). (1983) Risk assessment in the Federal Government: managing the process. Washington, DC: National Academy Press.

NIOSH. (1991) A quantitative assessment of the risk of cancer associated with exposure to 1,3-butadiene, based on a low dose inhalation study in B6C3F$_1$ mice. Submitted to the Occupational Safety and Health Administration (OSHA) for Butadiene Docket (#H-041). U.S. Department of Health and Human Services, Washington, DC.

NTP. (1998) National Toxicology Program Historical Controls Database. http://ehis.niehs.nih.gov.

Parker, WA; Barr, JR. (1951) Potassium bromate poisoning. Br Med J 1:1363.

Quick, CA; Chole, RA; Mauer, SM. (1975) Deafness and renal failure due to potassium bromate poisoning. Arch Otolaryngol 101:494-495.

Sai, K; Takagi, A; Umemura, T; et al. (1991) Relation of 8-hydroxydeoxyguanosine formation in rat kidney to lipid peroxidation, glutathione level and relative organ weight after a single administration of potassium bromate. Jpn J Cancer Res 82(2):165-169.

Sai, K; Hayashi, M; Takagi, A; et al. (1992a) Effects of antioxidants on induction of micronuclei in rat peripheral blood reticulocytes by potassium bromate. Mutat Res 269(1):113-118.

Sai, K; Uchiyama, S; Ohno, Y; et al. (1992b) Generation of active oxygen species in vitro by the interaction of potassium bromate with rat kidney cell. Carcinogenesis 13(3):333-339.

Sai, K; Umemura, T; Takagi, A; et al. (1992c) The protective role of glutathione, cysteine and vitamin C against oxidative DNA damage induced in rat kidney by potassium bromate. Jpn J Cancer Res 83(1):45-51.

Sai, K; Tyson, CA; Thomas, DW; et al. (1994) Oxidative DNA damage induced by potassium bromate in isolated rat renal proximal tubules and renal nuclei. Cancer Lett 87:1-7.

Sax, NI; Lewis, RJ. (1989) Dangerous properties of industrial materials. New York: Van Nostrand Reinhold.

Speit, G; Haupter, S; Schutz, P; et al. (1999) Comparative evaluation of the genotoxic properties of potassium bromate and potassium superoxide in V79 Chinese hamster cells. Mutat Res 439:213-221.

Tanaka, K; Oikawa, K; Fukuhara, C; et al. (1984) Metabolism of potassium bromate in rats: II. In vitro studies. Chemosphere 13:1213-1219.

U.S. Environmental Protection Agency (U.S. EPA). (1986a) Guidelines for carcinogen risk assessment. Fed Reg 51(185):33992-34003.

U.S. EPA. (1986b) Guidelines for the health risk assessment of chemical mixtures. Fed Reg 51(185):34014-34025.

U.S. EPA. (1986c) Guidelines for mutagenicity risk assessment. Fed Reg 51(185):34006-34012.

U.S. EPA. (1988) Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008, NTIS PB88-179874/AS, February 1988.

U.S. EPA. (1991) Guidelines for developmental toxicity risk assessment. Fed Reg 56(234):63798-63826.

U.S. EPA. (1994a) Interim policy for particle size and limit concentration issues in inhalation toxicity: notice of availability. Fed Reg 59(206):53799.

U.S. EPA. (1994b) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U.S. EPA. (1994c) Peer review and peer involvement at the U.S. Environmental Protection Agency. Signed by the U.S. EPA Administrator Carol M. Browner, dated June 7, 1994.

U.S. EPA. (1995) Guidance on risk characterization, memorandum from Carol Browner. March 21, 1995. http://www.epa.gov/ordntrnt/ORD/spc/rccover.htm

U.S. EPA. (1995a) Proposed guidelines for neurotoxicity risk assessment. Fed Reg 60(192):52032-52056.

U.S. EPA. (1995b) Use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007.

U.S. EPA. (1996a) Proposed guidelines for carcinogen risk assessment. Fed Reg 61(79):17960-18011.

U.S. EPA. (1996b) Reproductive toxicity risk assessment guidelines. Fed Reg 61(212):56274-56322.

U.S. EPA. (1998) 1998 Science policy council handbook: peer review. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-98-001.

Umemura, T; Sai, K; Takagi, A; et al. (1993) A possible role for cell proliferation in potassium bromate ($KBrO_3$) carcinogenesis. J Cancer Res Clin Oncol 119:463-469.

Umemura, T; Sai, K; Takagi, A; et al. (1995) A possible role for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. Carcinogenesis 16:593-597.

Warshaw, BL; Carter, MC; Hymes, LC; et al. (1985) Bromate poisoning from hair permanent preparations. Pediatrics 76(6):975-978.

Watanabe, T; Abe, T; Satoh, M; et al. (1992) Two children with bromate intoxication due to ingestion of the second preparation for permanent hair waving. Acta Paediatr Jpn 34(6):601-605.

Weast, RC, ed. (1985) CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press, Inc.

Wolf, DC. (1998a) Personal communication from Douglas Wolf, National Health and Environmental Effects Research Laboratory, U.S. EPA, to Vicki Dellarco, Office of Water, U.S. EPA. February 20, 1998.

Wolf, DC. (1998b) Personal communication from Douglas Wolf, National Health and Environmental Effects Research Laboratory, U.S. EPA, to Jennifer Jinot, National Center for Environmental Assessment, U.S. EPA. January 12, 1998.

Wolf, GW; Kaiser, L. (1996) Final report sodium bromate: short term reproductive and development toxicity study when administered to Sprague Dawley rats in the drinking water. Submitted to National Toxicology Program, Research Triangle Park, NC. NTP/NIEHS NO. NOI-ES-15323.

APPENDIX A
EXTERNAL PEER REVIEW: SUMMARY OF COMMENTS AND DISPOSITION

Disposition of Specific Charge Questions

Question 1. Are you aware of any other data/studies that are relevant (i.e., useful for hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?

Peer Review Comment: One reviewer described a genotoxicity study of potassium bromate by Speit et al. (1999) and recommended that this study be incorporated into the Toxicological Review.

Response: This study was reviewed by U.S. EPA and was added to Section 4.4.3 of the Bromate Toxicological Review and to Section II.A.4 of the IRIS summary.

Peer Review Comment: One reviewer recommended that the IARC assessment and classification of potassium bromate be described in the Toxicological Review.

Response: U.S. EPA has reviewed this information and it has been added to Section 4.6 of the Bromate Toxicological Review.

Peer Review Comment: One reviewer noted that a chronic study in B6C3F1 mice by S. Takayama was presented in Kurokawa et al. (1986) but not mentioned in the Toxicological Review.

Response: The Takayama study cited in Kurokawa et al. (1986) is a personal communication; therefore, it is not available for review. The Kurokawa paper does not provide enough description of the methods or results of the Takayama study to warrant including a separate discussion in the Toxicological Review.

Question 2. For RfD, RfC, and cancer, where applicable, have the most appropriate critical effects been chosen? For the cancer assessment, are the tumors observed biologically significant?

Peer Review Comment: One reviewer noted that "no oral RfD for bromate was presented because of lack of data available. This was correctly handled." However, another reviewer noted that "the IRIS summary on bromate does not determine a RfD, but the data from the Kurokawa studies need to be reconsidered."

Response: U.S. EPA has reconsidered the noncancer toxicity data for bromate and has developed a RfD based on kidney effects observed in DeAngelo et al. (1998). This assessment has been added to Section 5.1 of the Bromate Toxicological Review and to Section I.A of the IRIS summary. Although the Kurokawa et al. studies do qualitatively describe noncancer effects in the kidney, none of these studies provides enough information on the incidence or statistical significance of lesions, or on the shape of the dose-response curve for noncancer effects to allow a quantitative assessment.

Peer Review Comment: One reviewer recommended that the original Kurokawa study (Kurokawa et al., 1983) be cited in the Toxicological Review. She noted that in Kurokawa et al. (1983) potassium bromate produced large intestine tumors in both male and female rats. Therefore, she recommended that the Toxicological Review include a discussion of other brominated chemicals that cause intestinal/colon tumors in rats.

Response: EPA agrees that the Kurokawa et al. (1983) study should be presented in the Toxicological Review and has added a summary of the study to Section 4.2. However, EPA disagrees that a significant discussion of the large intestine tumors is warranted. Kurokawa et al. (1983) list several tumor sites that had absolute numbers of increased tumors, but none, except the kidney and mesothelium, were statistically significantly increased. In the rest of Kurokawa's studies, intestinal tumors were not observed, and none were observed in DeAngelo et al. (1998). Dr. Doug Wolf of the U.S. EPA and pathologist on the DeAngelo study, does not think that sites other than kidney, thyroid, and mesothelium are at risk for developing tumors from bromate (Wolf, personal communication). Therefore, EPA concludes that adding a discussion of other brominated chemicals that cause intestinal tumors will not contribute to an understanding of the carcinogenicity weight-of-evidence for bromate.

Question 3. For RfD, RfC, and cancer, have the appropriate studies been chosen as principal?

Peer Review Comment: One reviewer recommended that the Kurokawa et al. (1983) be cited in determining the RfD.

Response: See response under Question 2.

Question 4. Studies included in the RfD, RfC, and cancer under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, and any evidence corroborative of the critical effects as well as to establish the comprehensiveness of the database with respect to various endpoints. Should some studies be removed?

Peer Review Comment: One reviewer recommended that the finding of mesotheliomas and kidney, intestinal, thyroid, and other tumors should be discussed in more detail, including a discussion of other chemicals that have caused these tumors in rats.

Response: It is only appropriate to compare bromate with other chemicals that cause the same tumors if there is enough information on structure activity relationship to bromate to determine whether they have a similar mode of action. Although limited information is available on bromate's mode of action, it appears that other chemicals that cause the same tumors as bromate may act through different modes of action. Therefore, it was determined to be inappropriate to include a discussion of other chemicals.

Question 5. Are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support the use of different (default) values than those proposed?

Peer Review Comment: One reviewer indicated that it may be useful to review/discuss the risk analysis that supports the use of potassium bromate as a food additive, especially in baking bread.

Response: EPA has searched the Food and Drug Administration's (FDA's) latest updated Generally Recognized as Safe list, and potassium bromate is not listed. A personal communication with FDA staff indicated that levels of bromate were set for white flour, wheat flour, malts, etc., and varied depending on the food product but were in the range of 50–75 ppm in the flours. No information is available on whether risk assessment was used to set these

levels. However, several studies (cited in DeAngelo et al., 1998) indicate that the baking process converts $KBrO_3$ to KBr, leaving little bromate in baked bread products. Therefore, any risk assessment done to support levels of bromate in flour are not likely to be relevant to an environmental exposure situation.

Peer Review Comment: One reviewer recommended that the Toxicological Review should note that there is a good correlation with asbestos and the occurrence of mesotheliomas in rats after experimental exposures with asbestos and the occurrence of mesotheliomas in humans after accidental/industrial exposure to asbestos.

Response: According to Dr. Doug Wolf, U.S. EPA/ORD/NHEERL, asbestos-induced mesotheliomas are not a relevant comparison. The tumors that arise from asbestos and other fibers are dependent not only on the composition of the fiber, but also on the size and shape of the fiber. The mechanism is likely very different. Also, fiber-induced mesotheliomas arise in the thoracic cavity, from the pleura, and rarely if ever cross the diaphragm. The bromate-induced mesotheliomas arise from the tunica vaginalis of the testicle, which apparently is a particular site for these tumors to arise in the male F344 rat. These mesotheliomas do not cross the diaphragm into the thoracic cavity. See this recent paper: Crosby, LM; Morgan, KT; Gaskill, B; et al. (2000) Origin and distribution of potassium bromate-induced testicular and peritoneal mesotheliomas. Toxicol Pathol 28:253-266.

Question 6. Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the principal study as well as the comprehensiveness of the data? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Peer Review Comment: One reviewer indicated that an oral RfD should be developed for bromate based on the available studies.

Response: EPA agrees. See response to comment on Question 2.

Question 7. Is the weight of evidence for cancer assigned at the appropriate level (where applicable)?

Peer Review Comment: One reviewer indicated that a discussion of the IARC classification of potassium bromate should be added to the Toxicological Review.

Response: EPA agrees. See response to comment on Question 1.

Peer Review Comment: One reviewer indicated that the cancers induced in rats by potassium bromate are significant and that these and other studies should be used to develop an RfD.

Response: EPA agrees that data are available to develop an oral RfD for bromate; see response to comment on Question 2. However, note that a RfD is developed on the basis of noncancer endpoints. For bromate, the kidney appears to be the target organ, with urothelial hyperplasia as the critical effect.