Bromate; CASRN 15541-45-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Bromate

File First On-Line 06/06/2001

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	06/06/2001*
Inhalation RfC (I.B.)	qualitative discussion	06/06/2001*
Carcinogenicity Assessment (II.)	yes	06/06/2001*

*A comprehensive review of toxicological studies was completed (July 17, 2006) - please see sections I.A.6., I.B.6., and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bromate
CASRN — 15541-45-4
Last Revised — 06/06/2001

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. 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. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Renal effects: Urothelial hyperplasia **Rat feeding study** **DeAngelo et al. (1998)**	NOAEL: 1.5 Mg KBrO$_3$/kg-day (1.1 mg BrO$_3^-$/kg-day) LOAEL: 7.9 mg KBrO$_3$/kg-day (6.1 mg BrO$_3^-$/kg-day)	300	1	4E-3 mg BrO$_3^-$/kg-day

*Conversion Factors and Assumptions -- Doses of potassium bromate were calculated by DeAngelo et al. (1998) on the basis of measured water consumption, body weight, and water concentrations. Potassium bromate doses were converted to bromate ion doses by multiplying by 0.766, the ratio of molecular weights for bromate ion (127.9) and potassium bromate (167).

I.A.2. Principal and Supporting Studies (Oral RfD)

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(5):587-594.

DeAngelo et al. (1998) administered potassium bromate in drinking water at concentrations of 0, 0.02, 0.1, 0.2, and 0.4 g/L and of 0, 0.08, 0.4, and 0.8 g/L to male F344 rats and male B6C3F1 mice (78/group), 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 by 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 by 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 was attributed to an excessive mesothelioma burden (Wolf, 1998a). The effects of potassium bromate 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 dose groups of 6.1 mg/kg-day and higher. The authors also observed foci of mineralization of the renal papilla and eosinophilic droplets in the proximal tubule epithelium, although no information on the dose levels for these findings was presented. No other treatment-related nonneoplastic effects were 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.

Results of DeAngelo et al. (1998) in male B6C3F1 mice indicate that mice may be less sensitive than rats to the effects of bromate exposure. 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 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 weight of male mice. Water consumption was decreased by 17% in the 59.6 mg BrO_3^-/kg-day dose group; this decrease was statistically significantly different from controls. Serum chemistry results were comparable between controls and treated mice, and no increased incidence of nonneoplastic lesion occurred in any tissue examined. Therefore, the highest dose tested, 59.6 mg BrO_3^-/kg-day, is a freestanding NOAEL in mice.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 300.

An uncertainty factor (UF) of 10 is applied to account for extrapolating from animals to humans and another 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 studies in two species and a multigeneration study. This results in a total uncertainty factor of 300.

MF = 1.

I.A.4. Additional Studies/Comments (Oral RfD)

Several cases of acute bromate intoxication have been reported in humans following accidental or suicidal ingestion of permanent hair wave neutralizing solutions (Benson, 1951; Parker and Barr, 1951; Quick et al., 1975; Gradus et al., 1984; Warshaw et al., 1985; Lue et al., 1988; Mack, 1988; Matsumoto et al., 1980; Lichtenberg et al., 1989; Watanabe et al., 1992). These products usually contain either 2% potassium bromate or 10% sodium bromate. The most common acute signs are severe gastrointestinal irritation (vomiting, pain, diarrhea) and the Central Nervous System depression (lethargy, hypotension, hypotonicity, 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.

Nakano et al. (1989) exposed male Wistar rats to 0.04% potassium bromate in drinking water for up to 15 months. If an intake of 0.1 L/kg-day is assumed, 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 in tubules of the inner medulla. Increased blood urea nitrogen (BUN), along with marked structural abnormalities of the cortical tubules, was noted after 15 months. Based on the decreased body weight gain and renal effects, this study identified a LOAEL of 30 mg BrO_3^-/kg-day, but did not identify a NOAEL.

Kurokawa et al. (1983) investigated the carcinogenicity of potassium bromate in the drinking water of F344 rats. Potassium bromate was administered to F344 rats (53/sex/group) at

concentrations of 0, 250, and 500 ppm for 110 weeks. (Equivalent doses of bromate ion were approximately 12 and 33 mg bromate/kg-day, estimated from average reported body weights and water consumption.) However, the 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. A variety of noncancer effects was reported, including 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 is provided on the incidence of these lesions or on the statistical significance of these findings; therefore, 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 in Kurokawa et al. (1986a) for male rats were 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day. 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 regarding the doses at which these changes were observed.

Kurokawa et al. (1986b) studied the carcinogenic potential of potassium bromate in both male and female F344 rats and female B6C3F1 mice. Potassium bromate in drinking water was administered to the animals. Time-weighted mean doses of potassium bromate were estimated by the authors based on 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 at approximately 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 non-neoplastic effects were described by the

authors. Significant decreases in serum chemistry, including glutamate pyruvate transaminase (GPT), 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.

The subchronic effects of bromate were evaluated in Kurokawa et al. (1990). Potassium bromate in water at concentrations of 0, 150, 300, 600, 1,250, 2,500, 5,000 or 10,000 ppm was administered to groups of F344 rats (10/sex/group) for 13 weeks. Daily doses corresponding to these concentrations are about 0, 16, 32, 63, 140, 270, 650, or 1,080 mg BrO_3^-/kg. 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 and above and significant increases of serum parameters (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, ALP, BUN, Na+, cholinesterase) in both sexes at 600 ppm. Serum potassium levels were significantly decreased. Droplets of various sizes and regenerative changes in the renal tubules were observed. This study identifies 63 mg/kg as an adverse effect level, but insufficient data were provided to determine whether effects occurred at lower doses.

In a study conducted for the National Toxicology Program, Wolf and Kaiser (1996) evaluated the potential reproductive and developmental toxicity of sodium bromate in Sprague-Dawley rats following oral administration in 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 22.0 mg BrO_3^-/kg-day.) Two groups of female rats were treated. The first group (10/dose group) was dosed from study days 1-34 to test for effects during conception and early gestation. The second group (13/dose group) was dosed from gestation day 6 to postnatal day 1 to test for effects during late gestation and birth. Male rats (10/group) were cohabitated with the second group for 5 days before dosing (study days 1-5) and were 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. 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. No treatment-related gross or microscopic changes occurred in the kidney, liver, spleen, testis, or epididymis. These results indicate that sodium bromate treatment does not produce any adverse signs of general toxicity at any of the dose levels tested, and on the

basis of these findings, a MTD was not reached. This study identifies a NOAEL of 80 ppm (7.7 mg BrO_3^-/kg-day) and a LOAEL of 250 ppm (22.0 mg BrO_3^-/kg-day) on the basis of changes in sperm density.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

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/developmental study for a second species and a multigeneration study. Reflecting medium confidence in the database, the confidence in the RfD is medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document: -- U.S. EPA, 2001

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included in Appendix A of the source. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — None

Agency Consensus Date 5/22/01

A comprehensive review of toxicological studies published through July 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for Bromate and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bromate
CASRN — 15541-45-4
Last Revised — 06/06/2001

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with an uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989) and, subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

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.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

None.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

None.

I.B.4. Additional Studies/Comments (Inhalation RfC)

None.

I.B.5. Confidence in the Inhalation RfC

None.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document - U.S. EPA, 2001

Other EPA Documentation — None

Agency Consensus Date 5/22/01

A comprehensive review of toxicological studies published through July 2006 indicated that there is insufficient health effects data to derive an RfC for Bromate at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bromate
CASRN — 15541-45-4
Last Revised — 06/06/2001

Section II provides information on three aspects of the carcinogenic assessment for the substance in question, the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of the 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 g/L drinking water or risk per g/cu.m air breathed. The third form in which risk is presented is the concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS background document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also use these Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the current *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986), bromate would be classified as B2, probable human carcinogen. 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. Three key studies (Kurokawa et al., 1986a, 1986b; DeAngelo et al., 1998) demonstrate the carcinogenicity of bromate in rats. All studies were well conducted, with an appropriate route of exposure and adequate numbers of animals. Several aspects of these bioassay studies support the conclusion that bromate has the potential to be a human carcinogen. 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. Whereas male rats had tumors at all three sites, only kidney tumors were observed in female rats. However, the kidney tumors in female rats developed in the absence of the significant toxicity observed in the male rats.

Second, a clear dose-response relationship existed in tumor incidence and in severity/progression of tumors. Kurokawa (1986a) observed a progression in severity from renal dysplastic foci, a preneoplastic lesion, through renal adenomas to renal carcinoma as the dose increased. Kurokawa et al. (1986b) observed dose-response relationships for kidney tumors in both male and female rats. Kurokawa (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.

There is some concern that the high dose in each of these studies exceeded the MTD for male rats. However, in all three studies, the decrease in survival began to appear relatively late in the study: at approximately week 70 in the Kurokawa et al. (1986a, 1986b) studies and at 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 were surviving 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 for high-dose groups these studies does not compromise these studies for use in risk assessment.

The evidence is too limited to give high confidence in a conclusion about any mode of carcinogenic action. Oxidative stress may play a role in the formation of kidney tumors, but the evidence is insufficient to establish lipid peroxidation and free-radical production as the key events responsible for the induction of kidney tumors. In addition, no data are currently available to suggest any mechanism for the production of thyroid tumors and mesotheliomas by bromate. Bromate is mutagenic in both rats and mice in vivo and in vitro assays; albeit, the testing has been limited to the Ames assay and in vitro cytogenetics and bone marrow assays. Given the limited data on the possible mechanism 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, the uncertainty surrounding the mode of action, and the inconsistency between the rat and mouse results, the human relevance of the rat data relies on the assumption that rat data, in general, are relevant to humans. In the absence of

a biologically based model, the assumption of low-dose linearity is considered to be a reasonable public health protective approach for estimating the potential risk for bromate because of the limited data on its mode of action and because of some evidence of mutagenicity.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Sufficient. Oral exposure to bromate results in an increased incidence of renal tubular tumors in male and female rats and an increased incidence of mesotheliomas and thyroid follicular cell tumors in male rats. 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 in Kurokawa et al. (1986a) for male rats were 0, 0.7, 1.3, 2.5, 5.6, 12.3, or 33 mg BrO_3^-/kg-day. 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. A statistically significantly increased incidence was observed for dysplastic foci at doses of 1.3 mg BrO_3^-/kg-day and above (incidence is 0/19, 1/19, 5/20, 6/24, 12/24, 19/20, and 19/20 for the 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day dose groups, respectively), for kidney tumors at doses of 5.6 mg BrO_3^-/kg-day dose group and above (incidence is 0/19, 0/19, 0/20, 1/24, 5/24, 5/20, and 9/20 for the 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day dose groups, respectively) and for the thyroid tumors (incidence is 0/19, 0/19, 0/20, 1/24, 0/24, 3/20, and 7/20 for the 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day dose groups, respectively) and mesotheliomas (incidence is 0/19, 0/19, 3/20, 4/24, 2/24, 3/20, and 15/20 for the 0, 0.7, 1.3, 2.5, 5.6, 12.3, and 33 mg BrO_3^-/kg-day dose groups, respectively) 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 in drinking water was

administered to the animals. Time-weighted mean doses of potassium bromate were estimated by the authors based on 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 at approximately 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. Treatment-related, statistically significant tumors observed in rats included renal cell adenomas and carcinomas and peritoneal mesotheliomas (in males only). The incidence of kidney tumors was 3/53, 32/53, and 46/53 in male rats and 0/47, 28/50, and 39/49 in female rats for the control, low-dose, and high-dose groups, respectively. The incidence of mesotheliomas in male rats was 6/53, 17/52, and 28/46 for the control, low-dose, and high-dose groups, respectively. The authors note that a "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 differences in tumor incidence between exposed and control animals were 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.

DeAngelo et al. (1998) administered potassium bromate in drinking water at concentrations of 0, 0.02, 0.1, 0.2, and 0.4 g/L and of 0, 0.08, 0.4, and 0.8 g/L to male F344 rats and male B6C3F1 mice (78/group), 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 by 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 by 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 was attributed to an

excessive mesothelioma burden (Wolf, 1998a). The effects of potassium bromate on survival and body weight in rats indicate that the MTD was reached in this study.

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 (incidence of adenomas and carcinomas combined is 1/45, 1/43, 6/47, 3/39, and 12/32 for the 0, 1.1, 6.1, 12.9, and 28.7 mg BrO_3^-/kg-day dose groups, respectively), thyroid (incidence of adenomas and carcinomas combined is 0/36, 4/39, 1/43, 4/35, and 14/30 for the 0, 1.1, 6.1, 12.9, and 28.7 mg BrO_3^-/kg-day dose groups, respectively), and *tunica vaginalis testis* (incidence of mesotheliomas is 0/47, 4/49, 5/49, 10/47, and 27/43 for the 0, 1.1, 6.1, 12.9, and 28.7 mg BrO_3^-/kg-day dose groups, respectively). 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; the thyroid tumors were first seen at 26 weeks.

Results of DeAngelo et al. (1998) in male B6C3F1 mice indicate that mice may be less sensitive than rats to the effects of bromate exposure. 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 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 weight of male mice. Water consumption was decreased by 17% in the 59.6 mg BrO_3^-/kg-day dose group; this decrease was statistically significantly different from controls. 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. (1983) investigated the carcinogenicity of potassium bromate in the drinking water of F344 rats. Potassium bromate was administered to F344 rats (53/sex/group) at concentrations of 0, 250, and 500 ppm for 110 weeks. (Equivalent doses of bromate ion were approximately 12 and 33 mg bromate/kg-day, estimated from average reported body weights and water consumption.) However, the 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.

II.A.4. Supporting Data for Carcinogenicity

Matsushima et al. (1986) investigated the carcinogenicity of $KBrO_3$ administered subcutaneously to newborn rats and mice. One group of 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/group) were given an intragastric dose of 300 mg/kg $KBrO_3$ (231 mg/kg BrO_3^-), 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 alone in the diet. 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/kg $KBrO_3$ (231 mg/kg BrO_3^-) 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. The occurrence of all tumors was significantly increased as treatment continued. 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 per 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.

Kurokawa et al. (1987) exposed 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 elsewhere 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 that 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.

The genotoxicity of bromate has been evaluated in a variety of in vitro and in vivo systems. It has tested positive in the *Salmonella typhimurium* assay in the presence of metabolic activation and in an in vitro test for chromosomal aberrations that uses 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 (Fuji 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). Bromate was cytotoxic, increased the frequency of cells with micronuclei, increased the number of chromosome aberrations, and increased DNA migration in a series of assays that used V79 Chinese hamster cells (Speit et al., 1999). Furthermore, potassium bromate clearly induced gene mutations at the HPRT locus of V79 Chinese hamster cells (Speit et al., 1999).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor — 7E-1 per (mg/kg-day)

II.B.1.2. Drinking Water Unit Risk* — 2E-5 per μg/L.

   *The unit risk should not be used if the water concentration exceeds 5E+2 µg/L, because
   above this concentration the unit risk may not be appropriate.

II.B.1.3. Extrapolation Method — Time-to-tumor, Weibull

   Drinking Water Concentrations at Specified Risk Levels

Risk Level	Concentration
E-4 (1 in 10,000)	5E+0 µg/L
E-5 (1 in 100,000)	5E-1 µg/L
E-6 (1 in 1,000,000)	5E-2 µg/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

   Tumor Type — testicular mesothelioma, renal tubular adenoma and carcinoma, and thyroid
   follicular cell adenoma and carcinoma
   Test Animals — F344 rats, male
   Route of Exposure — Ingestion, drinking water
   Reference — DeAngelo et al., 1998

Incidence[a]				
Administered dose (mg BrO_3^-/kg-day)	Human Equivalent Dose[b] (mg BrO_3^-/kg-day)	Testicular Mesothelioma	Thyroid Follicular Adenoma and Carcinoma	Kidney Adenoma and Carcinoma

		Incidence[a]		
0	0	0/71	0/60	1/69
1.1	0.3	4/73	4/63	1/67
6.1	1.7	5/73	2/67	6/71
12.9	3.5	11/71	5/58	3/62
28.7	7.9	31/67	17/54	18/56

[a]Includes tumor incidences from interim sacrifice groups.
[b]Human equivalent dose was estimated using body weight to the 0.75 power.

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)$^{-1}$]	q1*[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 human equivalent dose, obtained by body weight to the 3/4 power scaling factor, resulting in a 10% increase in cancer risk.
[b]95% lower confidence limit on estimated human equivalent dose resulting in a 10% increase in cancer risk.
[c]Unit cancer risk estimate based on drawing a straight line from the LED10 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.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Oral cancer risk was calculated based on the incidence of renal tubular tumors, thyroid follicular tumors, and testicular 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, that is, testicular mesotheliomas, kidney tubular adenomas and carcinomas, and thyroid follicular adenomas and carcinomas. Tumors were modeled for each site separately, and then the tumor site risks were combined to represent the total cancer risk. The multistage Weibull model was used in time-to-tumor analysis to help account for the early mortality in the highest dose groups. In the time-to-tumor analysis, tumor types are categorized as either fatal or incidental. Fatal tumors are those tumors thought to act rapidly to cause the animal to die, whereas incidental tumors are thought not to cause the death of the 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, t0 was set equal to 0. In addition, a one-stage model was the preferred model for each tumor type.

The highest cancer potency estimate for any individual tumor site was 0.54/mg/kg-day based on mesotheliomas. However, although time-to-tumor modeling 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 unit risk from multiple tumor sites, assuming the tumors at these different sites arise independently, the MLEs of low-dose cancer 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 using a Monte Carlo analysis. The 95% upper bound for the total unit risk was 0.70/mg BrO_3^-/kg-day. A sensitivity analysis based on the contribution to variance reported that the variability associated with the risk estimate for the mesotheliomas was contributing 85% of the variance of the sum.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

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 time-to-tumor model was selected because it can help account for the early mortality observed in treated animals as 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 statistically significant 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 than rats to the effects of bromate. 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.

The major limitation of the bromate hazard characterization is the lack of data on the effects of long-term exposure to bromate in humans. The available human data are limited to case reports of toxicity following acute, accidental ingestion. Therefore, to extrapolate rat tumor data for bromate to the human situation, it must be assumed that humans will respond like the rat. 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, there is not enough evidence to give high confidence in a conclusion about any mode of carcinogenic action. Some studies show that bromate is weakly mutagenic and causes chromosomal aberrations (Ishidate et al., 1984; Fujie et al., 1988; Hayashi et al., 1988; Hayashi et al., 1989; Sai et al., 1992a; Speit et al., 1999). The mode of action by which bromate induces mutations and, thus, tumors, in the target organs is uncertain. Some studies show that bromate may generate oxygen radicals, which increase lipid peroxidation 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 link this proposed mechanism to 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. Given the uncertainty about the mode of action, a science policy decision is made to use a low-dose linear extrapolation approach as 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.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Lack of data by the inhalation route of exposure for bromate precludes the development of a quantitative estimate of carcinogenic risk from inhalation exposure.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2001

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of in this IRIS Summary. A record of these comments is included in Appendix A of the source document. *To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)*.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date 5/22/01

A comprehensive review of toxicological studies published through July 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Bromate and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Bromate
CASRN — 15541-45-4

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None.

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Bromate
CASRN — 15541-45-4

Date	Section	Description
06/06/2001	I.A., II.,VI	RfD and carcinogenicity assessments, and RfC discussion first on line.
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
09/28/2006	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — Bromate
CASRN — 15541-45-4
Last Revised — 06/06/2001

- 15541-45-4

- Bromate
- Bromate(1-), bromochloro-, rubidium
- Bromic acid, potassium salt
- Bromic acid, sodium salt
- Bromic acid, zinc salt