Barium and Compounds; CASRN 7440-39-3

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 Barium and Compounds

File First On-Line 01/31/1987

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/11/2005
Inhalation RfC (I.B.)	qualitative discussion	03/30/1998
Carcinogenicity Assessment (II.)	yes	03/30/1998

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Barium and Compounds
CASRN — 7440-39-3
Section I.A. Last Revised — 07/11/2005

The RfD is an estimate of an exposure, designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a statistical lower confidence limit on the benchmark dose (BMDL), a no-observed-adverse-effect level (NOAEL), a lowest-observed-adverse-effect level (LOAEL), or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Since RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

An RfD of 7×10^{-2} mg/kg-day was previously entered on the IRIS data base in 1998. This value was based on a NOAEL of 0.21 mg/kg-day for the absence of a hypertensive effect in two human studies (Brenniman and Levy, 1984; Wones et al. 1990). The subchronic and chronic rat NTP (1994) studies, and the McCauley et al. (1985) study of unilaterally nephrectomized rats were used to support the identification of the kidney as a co-critical target. An uncertainty factor of 3 was used to account for data base deficiencies.

The change in the value of the RfD from the previous IRIS assessment is due to selection of a new principal study and critical effect, the use of benchmark dose modeling to determine the point of departure, and a new evaluation of both the literature and application of uncertainty factors.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	RfD
Nephropathy **2-year drinking**	$BMDL_{05}$: 63 mg/kg-day BMD_{05}: 84 mg/kg-day	300	0.2 mg/kg-day

Critical Effect	Experimental Doses*	UF	RfD
water study in mice **NTP (1994)**			

*Conversion Factors and Assumptions -
BMDL - 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to a 5% extra risk.
BMD - Maximum likelihood estimate of the dose corresponding to a 5% extra risk.

I.A.2. Principal and Supporting Studies

NTP (1994) exposed both sexes of F344/N rats and both sexes of B6C3F1 mice to barium chloride dihydrate ($BaCl_2 \times 2H_2O$) in drinking water for 13 weeks or 2 years. Drinking water concentrations in the chronic study (60 animals/sex/group) were and 0, 500, 1250, and 2500 ppm. The study authors estimated doses, using water consumption and body weight data, as 0, 15, 30, and 60 mg Ba/kg-day for male rats and 0, 15, 45, and 75 mg Ba/kg-day for female rats. The estimated doses for mice were 30, 75, and 160 mg Ba/kg-day for males and 40, 90, and 200 mg Ba/kg-day for females. In the subchronic study (10 animals/sex/group), drinking water concentrations were 0, 125, 500, 1000, 2000, and 4000 ppm. Estimated doses were 0, 10, 30, 65, 110, and 200 mg Ba/kg-day for male rats and 0, 10, 35, 65, 115, and 180 mg Ba/kg-day for female rats. For mice, the corresponding estimated doses were 0, 15, 55, 100, 205, and 450 mg Ba/kg-day for the males and 0, 15, 60, 110, 200, and 495 mg Ba/kg-day for the females. The animals were fed an NIH-07 diet. Barium was not reported as a contaminant of the feed.

Chemical-related nephropathy was observed in male and female mice following chronic or subchronic drinking water exposure to barium chloride. These lesions were characterized by tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and the presence of crystals, primarily in the lumen of the renal tubules. NTP pathologists concluded that these lesions were morphologically distinct from the spontaneous degenerative renal lesions commonly observed in aging mice. Survival rates were significantly reduced in the high dose group by 65% for males and 26% females when compared to controls. Mortalities were attributed to the chemical-related renal lesions (NTP, 1994). A significant number of chronically exposed mice in the high dose group had mild to severe cases of nephropathy, 19/60 males and 37/60 females. One female and two males in the intermediate dose group had mild to moderate cases of chemical-related nephropathy. Chemical-related nephropathy was also observed in rats following subchronic exposure. In the

chronic rat study, spontaneous nephropathy was observed in the majority of animals in both control and treatment groups precluding the detection of any treatment-related effect. Increased kidney weights were observed in male and female rats and female mice following 13 weeks of exposure. Female rats were the only animals with increased kidney weights following 15 months of exposure. See Section 4 of the Toxicological Review (U.S. EPA, 2005) for additional details.

The kidney appears to be the most sensitive target of toxicity resulting from repeated ingestion of soluble barium salts. Chronic and subchronic rodent studies conducted by NTP (1994) and McCauley et al. (1985) provide evidence for an association between barium exposure and renal toxicity. However, chronic and subchronic rodent studies conducted by Tardiff et al., (1980) and Schroeder and Mitchener (1975a, b) were unable to detect adverse effects, including renal toxicity, following exposure to barium. Unfortunately, no human studies have investigated the effects of barium exposure on the kidneys. The NTP (1994) 2-year drinking water study in B6C3F1 mice was selected as the principal study and chemical-related nephropathy was identified as the critical effect for deriving an RfD for barium and its soluble salts. The principal study and critical effect were selected after careful evaluation of all the available toxicity studies. The primary reason for selecting this study and critical effect was that the nephropathy data provide the best evidence of a dose-response relationship.

There is conflicting evidence whether or not barium exposure may induce hypertensive effects. An investigation of anesthetized dogs (Roza and Berman, 1971) infused with barium chloride at a rate of 2 µmol/kg/min reported an increase in mean blood pressure from 138/86 to 204/103 (n =24). In a series of subchronic and chronic drinking water studies, Perry et al. (1989, 1985) observed a hypertensive effect in rats receiving as little as 6 mg/kg-day. The animals in these studies were maintained on a low metal diet with lower concentrations of calcium and other minerals than standard rat chow. However, NTP (1994) found no association between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg-day). Likewise, McCauley et al. (1985) observed no adverse effect on blood pressure following subchronic exposure to barium in drinking water at the highest level tested (150 mg/kg-day).

The reduced concentrations of calcium and other minerals in the low metal diet has been identified as a possible reason for the discrepancy between the findings of Perry et al. (1989, 1985) and other animal studies that did not observe hypertension in barium-treated animals (NTP, 1994; McCauley et al.,1985). The calcium concentration in the low metal diet was 3.8 g/kg, while the nutritional requirement for maintenance, growth, and reproduction of rats is 5 g/kg (NRC, 1995). Perry has stated that the concentration of calcium in the diet was adequate for normal growth and development (Perry, 1984). It is, however, unclear if the reduced dietary concentrations of calcium may have contributed to development of barium-related

hypertension. There is some evidence that reduced dietary calcium is a risk factor for hypertension in humans (McCarron et al., 1984). In light of the possible association between reduced calcium intake and hypertension, and because hypertension has not been reported in animals receiving the recommended dietary concentration of calcium, the data from Perry et al. (1989, 1985) were not considered in the derivation of the RfD.

Acute hypertension has been observed in humans following accidental or intentional ingestion of soluble barium salts (CDC, 2003; Downs et al., 1995). Two human studies have investigated the effects of longer-term barium ingestion on blood pressure (Brenniman et al., 1981; Wones et al.,1990). Both investigations found no hypertensive effect with their highest exposure concentrations. Brenniman et al. (1981) found no effect on hypertension between two communities with a 70-fold difference in the barium concentrations of their drinking water. Wones et al. (1990) found no hypertensive effect in a before-and-after comparison of 11 subjects that were exposed to two concentrations of barium in their drinking water over the course of ten weeks. Coincidently, the same NOAEL of 0.21 mg/kg-day was identified for both studies. These NOAELs were estimated by EPA using standard estimates for drinking water intake (2 L/day) and average body weight (70 kg).

Neither Brenniman et al. (1981) nor Wones et al. (1990) provided sufficient data to support, or refute, the hypothesis that chronic barium exposure causes hypertension. Hypertension is a complex multifactorial condition and it is very possible that the effect of chronic barium exposure on blood pressure is relatively small compared to other determinates such as diet and exercise. Wones et al. (1990) attempted to control for the effect of diet by providing a standard diet to all of the study participants. Unfortunately, the power of this study was limited by the very small number of participants (n=11). They also used short exposure durations (4 weeks for each exposure concentration), which may not have been sufficient to observe a chronic effect. Brenniman et al. (1981) also examined a relatively small number of subjects (n=85) in the subpopulation that was controlled for key risk factors. Other limitations of Brenniman et al. (1981) were that they collected replicate blood pressure measurements from individuals during a single 20-minute period, they used community-wide exposure estimates, and they didn't control for a number of important risk factors for hypertension, including diet and exercise. In the absence of dose-response data for barium-induced hypertension the RfD was not based this effect.

The RfD was derived by the benchmark dose approach using renal lesions in mice as the critical effect from the NTP (1994) study. The benchmark response predicted to affect 5% of the population (BMR_{05}) was selected for the point of departure. Benchmark analysis (BMDS version 1.3.2) was used to model the incidence of chemical-related nephropathy in male and female mice (NTP, 1994). The BMD_{05} for males was 84 mg/kg-day and the lower 95% confidence limit (i.e., $BMDL_{05}$) was 63 mg/kg-day. The BMD_{05} for females was 93 mg/kg-

day and the $BMDL_{05}$ was 58 mg/kg-day. These $BMDL_{05}$ values are very similar, but since there is slightly less uncertainty in the estimate derived from the male mice (the BMD_{05} and $BMDL_{05}$ are closer together), the male $BMDL_{05}$ was used for deriving the RfD.

A lower BMR than 10% extra risk could be used because the critical effect was considered to be substantially adverse and distinctly chemical-related, and because the data range included a response lower than 10% (U.S. EPA, 2002). First, the lesions in the intermediate dose group (severity grades, mild to moderate) were intermediate on a continuum leading to severe nephropathy, with severity between that seen in the control group (maximum severity grade, minimal) and the high dose group (severity grades, mild to marked). Since the significantly reduced survival rate in the high dose group was associated with the chemical-related renal lesions (NTP, 1994), the effects in the intermediate dose group are considered possibly irreversible, and biologically significant. Further, a similar pattern of effects was evident in both males and females.

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

UF = 300

A total UF of 300 was applied: 10 for extrapolation for interspecies differences (UF_A: animal to human); 10 for consideration of intraspecies variation (UF_H: human variability); and 3 for deficiencies in the database (UF_D). A value of 10 for both the interspecies and intraspecies UFs is generally used in the absence of data to indicate otherwise. The rationale for application of the UFs is described below.

A 10-fold UF was used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). Insufficient information is available regarding the toxicity of chronic barium exposure to compare the dose-response relationship in animals with what could be expected in humans. No information was available to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans.

A 10-fold UF was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability). This UF was not reduced from a default of 10 because there are insufficient data on the dose-response relationship in humans and because there are studies in experimental animals that suggest gastrointestinal absorption may be higher in children than in adults (Taylor et al., 1962; Cuddihy and Griffith, 1972).

A 3-fold UF was used to account for uncertainty associated with deficiencies in the data base. The database of oral barium toxicity consists of two human studies, which found no effect on hypertension (Brenniman et al., 1981; Wones et al., 1990), and several chronic and subchronic

rodent studies. The database is deficient in several areas: neither a two-generation reproductive toxicity study nor an adequate investigation of developmental toxicity has been conducted. It is also not known if barium deposition in bone tissue is associated with an adverse effect. The available data indicate that renal toxicity is likely to be the most sensitive endpoint for chronic barium exposure.

An UF was not needed to account for subchronic- to-chronic extrapolation because a chronic study was used to derive the RfD. An UF for LOAEL-to-NOAEL extrapolation was not used since benchmark dose modeling was employed to determine the point of departure.

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

Several studies have investigated the hypertensive effect of barium in animals. Intravenous infusion of barium chloride into anesthetized dogs or guinea pigs resulted in increased blood pressure and cardiac arrhythmias (Hicks et al., 1986; Roza and Berman, 1971). Perry et al. (1989, 1985, 1983) were the only authors to report hypertension in animals following long-term ingestion of barium. The rats in this study were maintained on a rye-based diet with a calcium content below the recommended daily requirement (NRC, 1995). The diet was also lower in potassium than standard rat chow. Animals maintained on diets low in calcium or potassium may be more sensitive to the cardiovascular effects of barium. Acute effects of barium on the cardiovascular system have been shown to be modified by calcium and potassium (Shanbaky et al., 1978; Roza and Berman, 1971). Barium has also been shown to be a calcium agonist (U.S. EPA, 1990; WHO, 1990; Perry et al., 1989; Brenniman et al., 1981; Shanbaky et al., 1978). Potassium alleviates the cardiac effects and skeletal muscle effects associated with acute barium poisoning (U.S. EPA, 1990; WHO, 1990; Gould et al., 1973; Roza and Berman, 1971; Diengott et al., 1964). Perry and Erlanger (1982) observed that rats maintained on the rye-based diet and exposed to cadmium developed hypertension, whereas rats maintained on standard chow and exposed to cadmium did not. In view of a possible association between the barium-induced cardiovascular effects and calcium and potassium intake, the relevance of the data from Perry et al. (1983) to animals maintained on standard diets, or humans is uncertain.

NTP (1994) evaluated blood pressure and electrocardiogram readings of rats exposed to barium in drinking water for 13 weeks. No association was detected between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg-day). Likewise, McCauley et al. (1985) observed no adverse effect on blood pressure following administration of barium in drinking water at the highest level tested (150 mg/kg-day).

The uptake of barium in bone tissue was evaluated in F344/N rats sacrificed at the 15-month interim of the NTP (1994) 2-year drinking water study. Barium concentrations in upper, middle, and lower sections of the femur were increased by approximately three-orders of magnitude in the high dose groups when compared to controls. Minimal reductions in calcium concentrations were observed in the same femur sections and no effect on bone density was observed. The biological implications of increased barium deposition in the bone tissue is unclear. It is possible that barium may interfere with the physiological processes of bone tissue including white blood cell production. A significant reduction in mononuclear cell leukemia was observed in treated male rats (NTP, 1994). Addition research is needed to fully investigate potential osteogenic effects of elevated barium exposure.

Dietz et al. (1992) evaluated the reproductive toxicity of barium in rats and mice. A dose of approximately 200 mg/kg-day was associated with lower pregnancy rates in rats and mice. However, below normal pregnancy rates were observed in rats from both the treatment and control groups. A non-significant reduction in litter size was observed in rats that received an approximate dose of 200 mg/kg-day. In mice there was a significant reduction in litter size in animals receiving a dose of approximately 100 mg/kg-day, but the effect was not observed in the higher dose group. Birth weight in rat pups was significantly reduced in the 200 mg/kg-day treatment group, but no effect was observed on postnatal day 5. Based on this limited data set it is not clear if barium is associated with reproductive toxicity.

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 is medium. Medium confidence in the RfD reflects the high confidence in the principal study but medium confidence in the database. Confidence in the principal study is high because it is a high quality study conducted by the National Toxicology Program (NTP, 1994). The study included a control group and three exposure groups; each group contained 60 animals of both sexes. Standard NTP quality assurance and quality control procedures, including a review of all histology data by the Pathology Working Group, were employed. Confidence in the database is medium because it contains dose response data from chronic and subchronic animal studies, which indicate that renal toxicity is a sensitive endpoint in more than one species, and contains some limited reproductive data, but lacks data about developmental toxicity and other potentially adverse effects.

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 (2005). Toxicological review of barium in support of summary information on the Integrated Risk Information System.

This assessment was peer reviewed by a group of external scientists (May 2004). Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in ***Appendix A of the Toxicological Review of Barium and Compounds (U.S. EPA, 2005)***.

Agency Completion Date -- 06/27/2005

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 (email address).

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

Barium and Compounds
CASRN — 7440-39-3
Section I.B. Last Revised — 3/30/1998: not updated in the 2005 revision to the RfD

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 expressed in units of mg/m^3. In general, the RfC is an estimate (with 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

An RfC for barium is not recommended at this time. The human and animal inhalation and intratracheal studies suggest that the respiratory system is a target of barium toxicity. The data also suggest that systemic effects, such as hypertension, may occur following inhalation exposure. The human studies cannot be used to derive an RfC for barium because exposure concentrations were not reported. Although the NIOSH (1982) study measured barium breathing zone levels for some groups of workers, the barium exposure levels were not measured in the group of workers with the increased incidence of hypertension. The deficient reporting of the methods and results (in particular, the lack of information on the aerosol generation, number of animals tested, incidence data, and statistical analysis) of the only animal subchronic/chronic inhalation study (Tarasenko et al., 1977) precludes deriving an RfC for barium from animal data.

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

Several human studies have investigated the toxicity of inhaled barium compounds. Exposure to insoluble forms of barium such as barium sulfate and barite ore results in baritosis (Seaton et al., 1986; Doig, 1976; Pendergrass and Greening, 1953). Although profuse opacities are observed on the radiographs, no alterations in lung function, abnormal physical findings, or increases in the incidence of subjective symptoms have been reported. It appears that the accumulation of barium sulfate in the lungs will diminish upon termination of barium exposure. Barium exposure levels resulting in baritosis have not been reported. NIOSH (1982) reported an increased incidence of hypertension in workers exposed to an unspecified concentration of barium. Although the results of this study are consistent with the suggestion of hypertension following oral exposure to barium compounds, the results of the NIOSH (1982) study should be interpreted cautiously because it is likely that the workers were also exposed to other metals, including lead, which has a known hypertensive effect.

Inhalation toxicity data in animals are limited to inhalation exposure and intratracheal administration studies by Tarasenko et al. (1977) and an intratracheal administration study by Uchiyama et al. (1995). In the Tarasenko et al. (1977) inhalation study, a number of adverse effects was reported in rats exposed to 5.2 mg/m^3 barium carbonate (3.6 mg/m^3 barium) 4 h/day, 6 days/week for 4 months. The effects included alterations in some hematological and serum chemistry parameters, perivascular and peribronchial sclerosis with collagenation in the lungs, and increases in arterial pressure. It does not appear that statistical analysis of the data was performed, and incidence data for the lung effects were not reported. No adverse effects were observed in the rats exposed to 1.15 mg/m^3 barium carbonate (0.80 mg/m^3 barium). The finding of lung lesions following exposure to barium carbonate was confirmed by an intratracheal administration study conducted by Tarasenko et al. (1977). In this study, fibrous

pneumonia and necrosis of the mucous membrane of the large bronchi was observed 9 mo after animals received an intratracheal dose of 50 mg barium carbonate (35 mg barium). As with the inhalation study, the results of this study were poorly reported. Uchiyama et al. (1995) also found pulmonary effects (bronchopneumonia, bronchitis, or bronchiolitis) in rabbits intratracheally administered a suspension containing 85% barium sulfate. Although studies conducted by Tarasenko et al. (1977) suggest that inhalation exposure to barium carbonate may result in reproductive effects, confidence in these studies is very low because of poor reporting of study design and results. Thus, the potential of barium to induce developmental and/or reproductive effects following inhalation exposure has not been adequately assessed.

Human Studies

The database on the toxicity of inhaled barium compounds in humans consists primarily of studies of occupational exposure to barium sulfate or barite ore or to unspecified soluble barium compounds. Several case reports (for example, Seaton et al., 1986; Pendergrass and Greening, 1953) and a prospective study conducted by Doig (1976) have reported baritosis in barium-exposed workers. Baritosis is considered a benign pneumoconiosis resulting from the inhalation of barite ore or barium sulfate. The most outstanding feature of baritosis is the intense radiopacity of the discrete opacities, which are usually profusely disseminated throughout the lung fields; in some cases the opacities may be so numerous that they appear confluent. The Third Conference of Experts on Pneumoconiosis (ACGIH, 1992) noted that barium sulfate produced a noncollagenous type of pneumoconiosis that has a minimal stromal reaction and consists mainly of reticulin fibers, intact alveolar architecture, and potentially reversible lesions. The available human data on baritosis suggest that the accumulation of barium in the lungs does not result in medical disability or symptomatology. A decline in the profusion and opacity density, suggesting a decrease in the amount of accumulated barium in the lung, has been observed several years after termination of barium exposure. Studies by NIOSH (1982) and Zschiesche et al. (1992) on soluble barium compounds did not include radiography; these studies focused on the potential for barium to induce systemic effects (e.g., increases in blood pressure, kidney effects, EKG alterations).

Doig (1976) conducted a prospective study on workers at a barite grinding facility. During the initial investigation in 1947, 5 workers employed for more than 3.5 years were examined. No evidence of baritosis was observed in any of the workers. In 1961, 8 workers (aged 26-45 years, mean of 32 years) employed for 3.5-18 years (mean of 9 years) were examined (1 of these workers was also examined in 1947). Seven of the workers reported no respiratory symptoms; 1 worker reported a slight occasional cough. No abnormal findings were observed during the physical examination of 7 of the workers; crepitations dispelled by cough were observed in 1 worker (not the same worker reporting an occasional cough). Pneumoconiosis was detected in the radiographs of 7 workers. Three other workers employed for 1 month to 1

year were also examined in 1961. Two of these workers reported having slight coughs, but no abnormal findings were observed during the physical examination and the chest radiographs were normal. At this time, dust concentrations ranging from 2,734 to 11,365 particles per mL were measured using a thermal precipitator; the concentration of barium in the dust was not measured. Barite samples were analyzed for quartz, silica, and iron content. No quartz was detected, and the total silica and total iron (as Fe_2O_3) concentrations were 0.07%-1.96% and 0.03%-0.89%, respectively.

Ten of the 11 workers examined in 1961 were reexamined in 1963 (18 mo later). Two new cases of pneumoconiosis were diagnosed. Thus, 9 of 10 workers exposed to barium sulfate for 1.5 to 19.5 years (mean of 8.2 years) had well-marked baritosis. Three of these workers reported a slight or occasional cough and none had dyspnea. Among the 9 workers with baritosis, 3 did not smoke, 4 smoked <= 1 pack/day, and 2 smoked > 1 pack/day. In six of the seven workers with previously diagnosed baritosis, no significant changes in the degree of pneumoconiosis were observed; an increase in the number of opacities was observed in the seventh worker. Spirometric lung function tests (vital capacity, flow rate, and forced expiratory volume) were performed in five workers. For three of these workers, the results of the lung function tests were similar to predicted normal values (89%-119% of predicted values). Lung function was below normal in the other two workers (70%-85% of predicted values). It is questionable whether the impaired lung function was related to barium exposure. One of the two workers was an alcoholic and heavy smoker and the other had a fibrotic right middle lung lobe that probably resulted from a childhood illness.

In 1964, the barite grinding facility closed. Follow-up examinations were performed in 1966, 1969, and 1973 on five of the workers. Termination from barium exposure resulted in a decline in the profusion and density of opacities. In 1966, there was slight clearing of opacities; by 1973, there was a marked decrease in profusion and density. No significant changes in lung function were observed during this 10-year period.

NIOSH (1982) conducted a health survey of past and present workers at the Sherwin Williams Company's Coffeyville, KS, facility. Work performed at the facility included grinding, blending, and mixing of mineral ores. At the time of the study, four processes were in operation: "ozide process," which involved blending several grades of zinc oxide; "ozark process," which involved bagging very pure zinc oxide powder; "bayrite process;" which involved grinding and mixing several grades of barium-containing ores; and "sher-tone process," which involved mixing inert clays with animal tallow. A medical evaluation was performed on 61 current workers (91% participation) and 35 laid-off or retired workers (27% participation). Information on demographics, frequency of various symptoms occurring during the past 2 mo, chemical exposure, occupational history, smoking history, and histories of renal disease, allergies, and hypertension were obtained from directed questionnaires. In addition,

spot urine and blood samples and blood pressure measurements were taken. Exposures to barium, lead, cadmium, and zinc were estimated from 27 personal samples collected over a 2-day period. In the seven personal breathing zone samples collected from the bayrite area, the levels of soluble barium ranged from 87.3 to 1,920.0 µg/m^3 (mean of 1,068.5 µg/m^3), lead levels ranged from not detected to 15.0 µg/m^3 (mean of 12.2 µg/m^3, excluding the two no-detect samples), zinc levels ranged from 22.4 to 132.0 µg/m^3 (mean of 72 µg/m^3), and all seven samples had no detectable levels of cadmium. Soluble barium was also detected in breathing zone samples in the ozark area (10.6-1,397.0 µg/m^3; mean of 196.1 µg/m^3), ozide area (11.6-99.5 µg/m^3; mean of 46.8 µg/m^3), and sher-tone area (114.3-167.5 µg/m^3; mean of 70.5 µg/m^3).

Two approaches were used to analyze the results of the health survey. In the first approach, the workers were divided into five groups on the basis of current job assignments. Fourteen of the 61 current workers worked in the bayrite area. No statistically significant increases among the different groups of workers were observed in the incidence of subjective symptoms (e.g., headache, cough, nausea), or differences in mean blood lead levels, number of workers with blood lead levels of greater than 39 µg/dL, mean free erythrocyte protoporphyrin (FEP) levels, mean hematocrit levels, mean serum creatinine levels, number of workers with serum creatinine levels of greater than 1.5 mg/dL, number of workers with BUN levels of greater than 20 mg/dL, blood pressure, or mean urine cadmium levels.

In the second approach, the workers were divided into seven groups on the basis of past job assignments. One group consisted of 12 workers working in barium process areas (bayrite process and other processes no longer in operation at the facility that involved exposure to barium ores and barium carbonate) for at least 5 years; barium exposure levels were not reported for this group. The results of the health survey for the barium-exposed workers were compared with 25 workers who stated that they had never worked in barium process areas. No statistically significant differences between the groups were observed in mean age, number of years employed, number of current or past smokers, prevalence of subjective symptoms, mean FEP levels, mean hematocrit levels, mean urine cadmium levels, mean beta2-microglobulin levels, or the prevalence of workers with elevated serum creatinine, BUN, or urine protein levels. The number of workers with elevated blood pressure (defined as systolic pressure >= 140 mm Hg or diastolic pressure >= 90 mm Hg, or taking medication for hypertension) was significantly higher (p = 0.029) in the barium-exposed group (7/12, 58%) than in the comparison group (5/25, 20%). The number of workers in the barium group with blood lead levels of > 39 µg/dL was lower than in the comparison group (0% versus 28%); however, the authors determined the difference not to be statistically significant (p = 0.072). Additionally, there was no significant difference between mean blood lead levels in the barium-exposed workers (24 µg/dL) and the comparison group (32 µg/dL). Although the results of this study suggest an association between exposure to barium and hypertension, the results should be

interpreted cautiously because only a small number of workers was examined, it appears that blood pressure was only measured once, and the workers were exposed to a number of other chemicals, including lead, which is associated with an increase in blood pressure.

The health effects associated with occupational exposure to barium during arc welding with barium-containing stick electrodes and flux-cored wires were investigated by Zschiesche et al. (1992). A group of 18 healthy welders not using barium-containing consumables in the past 10 days were divided into three groups: group A (n = 8, mean age of 30.4 years) performed arc welding with barium-containing stick electrodes, group B (n = 5, mean age of 43.6 years) performed arc welding with barium-containing self-shielded flux-cored wires, and group C (n = 5, mean age of 32.0 years) performed arc welding with barium-containing self-shielded flux-cored wires using welding guns with built-in ventilation systems. All welders performed welding with barium-free consumables on Thursday and Friday of the first week of the study. Barium-containing consumables were used during week 2 of the study and on Monday of week 3. The subjects welded for an average of 4 h per day. The average barium concentrations in the breathing zones were 4.4 (range of 0.1-22.7), 2.0 (0.3-6.0), and 0.3 (0.1-1.5) mg/m^3 for groups A, B, and C, respectively. No exposure-related subjective symptoms of health or neurological signs were found. No significant differences between pre and postshift EKG, pulse rate, whole blood pH, base excess and standard bicarbonate, and plasma concentrations of sodium, magnesium, and total and ionized calcium were observed. During week 2, decreases in plasma potassium concentrations were observed in groups A and C; the levels returned to the normal range under continuation of barium exposure and were not statistically different from levels during week 1 (no barium exposure). This drop in serum potassium levels was not observed in group B, which had a barium exposure level similar to group A.

Animal Studies

Data on the toxicity of barium compounds in animals following inhalation exposure is limited to a subchronic study conducted by Tarasenko et al. (1977). In this study, male albino rats (strain and number of animals per group not reported) were exposed to 0, 1.15, or 5.20 mg/m^3 barium carbonate (0, 0.8, or 3.6 mg Ba/m^3) 4 h/day, 6 days/week for 4 months. No information on aerosol generation or the size distribution of the particles was reported. In the introduction section of the paper, the authors state, "we have demonstrated by electron microscopy that the size of almost 80% of the dust particles is less than 2 μm"; however, it is not known if this statement refers to the aerosols generated for this study. The following endpoints were used to assess toxicity: body weight gain, arterial pressure, hematology (hemoglobin, leukocytes, and thrombocytes) and serum chemistry (glucose, phosphorus, total protein, alkaline phosphatase, and cholinesterase) parameters, urine calcium levels, bromosulfophthalein test of liver function, electrocardiogram measurement, and histologic examination (tissues examined were not listed).

The authors noted that no alterations were observed in the rats exposed to 1.15 mg/m^3 barium carbonate. In the 5.20 mg/m^3 group, a number of alterations were reported; however, it does not appear that the data were statistically analyzed. The alterations included a 21% decrease in body weight gain, a 32% increase in arterial pressure, altered hematological parameters (decreases in hemoglobin and thrombocyte levels and increases in leukocyte levels), altered serum chemistry parameters (decreased sugar and total protein levels, increased phosphorus levels, decreased alkaline phosphatase activity, and increased cholinesterase activity), increased calcium levels in the urine, impaired liver function, and histologic alterations in the heart, liver, kidneys, and lungs. No alterations in the EKG readings were reported. However, when the rats were administered proserine, the EKG reading suggested disturbances in heart conductivity. The authors noted that the heart, liver, and kidneys "had a character of mild protein ('granular') dystrophy." In the lungs, the histologic alterations consisted of moderate perivascular and peribronchial sclerosis with focal thickening of the intraalveolar septa and collagenation. No incidence data were provided.

In another study conducted by Tarasenko et al. (1977), animals (it appears that albino rats and rabbits were tested; number of animals not specified) were administered an intratracheal dose of 50 mg barium carbonate (35 mg barium). Three months after administration, sclerotic changes were observed in the lungs. The severity of the sclerosis progressed. At 9 mo, fibrous pneumonia with necrosis of mucous membranes of the large bronchi was observed.

Uchiyama et al. (1995) administered a single intratracheal dose of 0.015, 0.3, or 0.6 mL/kg of BA147 to rabbits. BA147 is a preparation containing 85% barium sulfate. No treatment-related effects on pulmonary ventilation (measured 1 day, 3 days, and 1, 2, and 4 weeks after dosing), levels of blood gases (measured at the same time as pulmonary ventilation), or lung weights were observed. Soft X-rays of the lungs revealed dose-related shadows. Bronchopneumonia, bronchitis, or bronchiolitis was observed in 28 of 36 animals during the first week after dosing. Thereafter, the alterations were not observed. No further details of this study were available because the study was published in a Japanese-language journal; information on the study was obtained from an English abstract.

Information on the reproductive/developmental toxicity of inhaled barium compounds is limited to a series of studies conducted by Tarasenko et al. (1977). The results of these studies were described in general terms and no data were provided. The poor reporting of the study design and results and the lack of statistical analysis of the data limit the usefulness of the data for assessing the reproductive/developmental toxicity of barium.

Exposure of male rats to 22.6 mg/m^3 barium carbonate (15.7 mg Ba/m^3) for one cycle of spermatogenesis (daily exposure duration and frequency of exposure were not reported) resulted in decreases in the number of spermatozoids, percentage of motile forms and time of

motility, osmotic resistance of spermatozoids, increases in the number of ducts with desquamated epithelium, and a reduced number of ducts with 12th stage meiosis (Tarasenko et al., 1977). Similar results were observed in rats exposed to 5.2 mg/m^3 barium carbonate (3.6 mg Ba/m^3) 4 h/day, 6 days/week for 4 months.

Tarasenko et al. (1977) also reported that a shortening of the mean duration of estrous cycle and an alteration in the proportion of mature and dying ovarian follicles were observed in rats exposed to 13.4 mg/m^3 barium carbonate (9.3 mg Ba/m^3) for 4 months (duration of daily exposure or frequency of exposure was not reported), as compared to a control group. These effects were not observed in rats exposed to 3.1 mg/m^3 (2.2 mg Ba/m^3). The authors also noted that rats in the 13.4 mg/m^3 group gave birth to underdeveloped offspring that showed considerable mortality and slow increases in body weight during the first two months of life. The authors did not state whether the barium carbonate-exposed females were mated to exposed or unexposed males.

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

Not applicable.

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

Not applicable.

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

I.B.5. Confidence in the Inhalation RfC

Not applicable.

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

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

Source Document — U.S. EPA, 2005.

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 as an appendix to the Toxicological Review of Barium and Compounds

(CAS No. 7440-39-3) in support of summary information on IRIS (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date — 2/18/1998

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Barium and Compounds conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Barium and Compounds
CASRN — 7440-39-3
Section II Last Revised — 3/30/1998: not updated in the 2005 revision to the RfD

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 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. The third form in which risk is presented is a concentration of the chemical in drinking water or air providing 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 utilize those 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 EPA's 1986 Guidelines for Carcinogen Risk Assessment, barium would be classified as Group D, not classifiable as to human carcinogenicity. Although adequate chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled barium.

Under the Proposed Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996), barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure.

Basis — Oral exposure studies in rats and mice (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a, b) did not find significant increases in tumor incidence following chronic exposure. In the NTP (1994) rat study, statistically significant negative trends in the incidence of leukemia, adrenal tumors, and mammary gland tumors were observed. The design of the rat and mouse NTP (1994) studies was adequate to assess carcinogenicity. These studies used an adequate number of animals per group, exposed animals for 2 years, tested several dosage levels, and examined an extensive number of tissues.

The inhalation exposure and intratracheal studies conducted by Tarasenko et al. (1977) are inadequate for carcinogenicity evaluation because of several deficiencies in the design and reporting, including single or subchronic exposure duration, inadequate reporting of aerosol generation methodology, inferior reporting of study results (including the apparent lack of statistical analysis), and the use of only one sex (males). These studies were designed to be toxicity studies, and it is not known if the investigators looked for tumors.

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

Inadequate. The only available human carcinogenicity data are two topical application studies conducted by Ayre (1966) and Ayre and LeGuerrier (1967). These studies involved a single topical application of barium chloride to the cervix of one woman.

In a study to determine the safety of components of intrauterine contraceptive devices, a single topical application of 1.25 mM barium chloride was applied to the squamocolumnar junctional area of the cervix of a woman with no known history of abnormal cervical cytology results (Ayre, 1966; Ayre and LeGuerrier, 1967). A cervical cell scraping was performed 48 h after application. The topical application of barium chloride and cervical cell scraping was repeated four times at intervals of 4-6 weeks. A number of cell transformations resembling severe premalignant dysplasia were observed; the transformed cells were described as bizarre, multinucleated cells with profoundly altered nuclear chromatin. One to three weeks after barium chloride application, these cellular alterations were no longer observed.

In another study (Ayre, 1966; Ayre and LeGuerrier, 1967), 1.25 mM barium chloride was mixed with equal amounts of 70% DMSO and a single topical application of the mixture was applied to the squamocolumnar junctional area of the cervix. It is assumed that only one subject was used, and it was not reported whether this was the same woman previously tested. Cervical scrapings were performed after 48 h, 72 h, and twice weekly for an unspecified amount of time. The cell transformations were similar to extreme dysplasia; in addition, spindle cells and cells with marked hyperchromatism with multiple chromatin bundles and enlarged irregular nucleated forms were observed. Cell transformations were also observed in deeper layers of the squamous epithelium. The authors noted that the transformed cells resembled cell findings of cancer *in situ*. Sixteen days after topical application, the cell transformations were not observed in the deeper layers of the epithelium, but were still present in superficial and intermediate areas.

II.A.3. Animal Carcinogenicity Data

Oral Exposure. Sufficient. Four animal studies evaluated the carcinogenicity of barium (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b) in rats and mice. The design of NTP (1994) rat and mouse studies was adequate for carcinogenicity evaluation.

In a chronic study conducted by NTP (1994), male and female B6C3F1 mice (60 animals/dose group/sex) received barium chloride dihydrate in drinking water at concentrations of 0, 500, 1250, or 2500 ppm for 103 weeks (males) and 104 weeks (females). The authors estimated the daily doses for the treated groups using measured water consumption and body weights as 0, 30, 75, and 160 mg Ba/kg-day for males, and 0, 40, 90, and 200 mg Ba/kg-day for females.

The animals were fed an NIH-07 mash diet; the barium content of the diet was not reported. At the 15-month interim evaluation, venous blood was collected from all mice for hematology and clinical chemistry. In addition, a limited number of mice (9, 10, 10, and 10 males and 10, 7, 10, and 6 females from the 0, 500, 1250, and 2500 ppm groups, respectively) were sacrificed at 15 months. The remaining animals continued on the study until they were moribund, died naturally, or were sacrificed at the end of the study. Necropsy and complete histopathologic examinations were performed on all animals. Body weights were monitored and organ weights were determined at 15 months.

At 2500 ppm, the survival percentages for mice at the end of study (65% for males and 26% for females) were significantly lower than those of the controls (89% males; 76% females). The reduction in survival became apparent in females at week 15 and in males at week 65, and was attributed to chemical-related renal lesions. At the lower dose levels survival was not significantly lower than in controls. In male and female high-dose mice, the final mean body weights were 8% and 12% lower, respectively, than those of the corresponding control groups. Water consumption was not affected by barium.

At the 15-month interim evaluation, the absolute and relative spleen weights of the female mice that received 2500 ppm were significantly lower than those of the controls, and the absolute and relative thymus weights of high-dose male mice that received 2500 ppm were marginally lower than those of the controls. Determination of hematology and clinical chemistry parameters (e.g., phosphorus, calcium, and urea nitrogen) at the 15-month interim evaluation showed no significant differences between control and exposed mice.

The incidence of nephropathy at the end of the study was significantly increased in mice receiving 2500 ppm. There were no other chemical-related noncarcinogenic histologic changes. The incidence of neoplasms in the barium-exposed mice was not significantly higher than in control mice. In the 2500 ppm female mice, the incidence of several neoplasms was significantly lower than in the controls; the authors attributed this finding to the marked reduction in survival in the barium-exposed animals.

In the same chronic study (NTP, 1994), male and female F344/N rats (60 animals/dose group/sex) received drinking water containing 0, 500, 1250, or 2500 ppm barium chloride dihydrate for 104 weeks (males) or 105 weeks (females). The authors estimated daily doses for the treated groups using measured water consumption and body weights as 0, 15, 30, and 60 mg Ba/kg-day for males, and 0, 15, 45, and 75 mg Ba/kg-day for females. The animals were fed an NIH-07 mash diet; the barium content of the diet was not reported. For a 15-month interim evaluation, venous blood was collected from all rats for hematology and clinical chemistry. In addition, a limited number of rats (10 from each group) were sacrificed at 15 months. The remaining animals stayed on the study until they were moribund, died

naturally, or were terminally sacrificed. Necropsy and complete histopathologic examinations were performed on all animals. Body weights were monitored throughout the study, and organ weights were determined in the animals killed at 15 mo.

A marginally increased survival of exposed male groups (percent of survival: 62%, 58%, and 67% for the 500, 1250, and 2500 ppm groups, respectively) was observed compared with that of the male controls (44%). Survival of the females was not significantly affected. For male rats receiving 2500 ppm the final mean body weights were 5% lower than for controls. The final mean body weights of females receiving 1250 and 2500 ppm were 6% and 11% lower, respectively, than those of controls. Water consumption was decreased in a dose-related manner; at the highest exposure level the decrease, relative to controls, was 22% in males and 25% in females.

Absolute and relative organ weights, determined only at the 15-month interim evaluation, were not affected in the males. In the females, a decrease in the absolute liver weight and an increase in the relative kidney weights occurred at 2500 ppm. Body weights in the females at 15 months were decreased by 9% at 2500 ppm in comparison with controls, whereas kidney weights in this group were slightly increased relative to controls. Determination of hematology values and clinical chemistry values (e.g., phosphorus, calcium, and urea nitrogen) at the 15-month interim evaluation showed no significant differences between control and exposed rats.

No chemical-related noncarcinogenic histologic changes were observed in any organs or tissues. No statistically significant increases in the incidence of neoplasms were observed in the barium-exposed rats. Significant negative trends were observed in the incidence of mononuclear cell leukemia in male rats (35/50, 25/50, 26/50, and 15/50 in 0, 500, 1250, and 2500 ppm groups, respectively), benign and malignant adrenal medulla pheochromocytoma in male rats (13/49, 11/50, 12/49, and 6/50, respectively), and mammary gland neoplasms (fibroadenoma, adenoma, or carcinoma) in female rats (17/50, 21/50, 13/50, 11/50, respectively). Cancer incidences that were significantly lower than in controls were reported for mononuclear cell leukemia in male rats exposed to 500, 1250, and 2500 ppm, and adrenal medulla pheochromocytoma in male rats exposed to 2500 ppm.

In a study by McCauley et al. (1985), CD Sprague-Dawley rats were fed Purina rat chow containing 12 ppm barium. The three exposure regimens were as follows: (1) male CD Sprague-Dawley rats (12/group) were exposed to 0, 1, 10, 100, or 250 ppm barium (barium chloride) in drinking water for 36 weeks; (2) female CD Sprague-Dawley rats (12/group) were exposed to 0 or 250 ppm for 46 weeks; and (3) male CD Sprague-Dawley rats (10/group) were exposed to 0, 1, 10, or 100 ppm barium in drinking water for 68 weeks. The authors reported that no significant differences in food or water intake or body weight were observed, but did not report the actual data. They stated that rats that received 10 ppm of barium in the drinking

water ingested 1.5 mg Ba/kg-day from water and 1 mg Ba/kg-day from the Purina diet. This barium intake was used to estimate total barium intake for the other exposure levels. Thus, the estimated total barium intakes were 1, 1.15, 2.5, 16, and 38.5 mg/kg-day for the 0, 1, 10, 100, and 250 ppm concentrations for all exposure regimens.

The authors did not comment on whether there were any effects on survival. Histologic evaluations of an extensive number of tissues, including gastrointestinal tract, liver, heart, adrenal gland, brain, respiratory tract, spleen, thymus, kidneys, ovaries, and testes, did not reveal barium-related lesions. No alterations in hematocrit levels were observed. A retinal lesion (focal absence of the outer layers of the retina) was observed in 5/12 males exposed to 100 ppm but 0/11 males exposed to 250 ppm for 36 weeks, 7/12 females exposed to 250 ppm for 46 weeks, 1/10 male controls exposed for 68 weeks, and 2/10 males in each of the 1, 10, and 100 ppm groups exposed for 68 weeks. Because this lesion does not appear to be dose or duration-related, its relationship to barium exposure is uncertain. No significant increases in the incidence of neoplasms were observed in the barium-exposed rats, but the study was shorter than lifetime and would have missed late-developing tumors.

Schroeder and Mitchener (1975a) exposed Long-Evans rats (52/sex/group) to 0 or 5 ppm barium (barium acetate) in drinking water from weaning to natural death. Dosages from drinking water were calculated as 0.61 mg Ba/kg-day for males and 0.67 mg Ba/kg-day for females based on reference values for body weights and water intake from U.S. EPA (1988). The diet was characterized as a "low- metal" diet and included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized table salt, and assorted vitamins; the barium content was not reported. Barium had no significant effect on the growth of males, but increased the growth of older females. The life span of the rats was not significantly affected. The incidence of proteinuria in males exposed to barium for approximately 152 days (at 173 days of age) was significantly ($p < 0.05$) higher than in controls; proteinuria was assessed by a dipstick method and the magnitude was not reported. Female rats at 532 and 773 days of age had higher ($p < 0.001$) serum cholesterol concentrations than controls tested at 516 and 769 days of age. Serum glucose levels for males at these ages were also different from controls but did not follow an age-related pattern. The authors attached no biological or toxicological significance to these serum chemistry results. Histopathology of heart, lung, kidney, liver, and spleen did not reveal alterations. No significant increases in the number of gross tumors were observed in the barium-exposed male (8/30) or female (15/33) rats as compared to the controls (4/26 and 17/24 for males and females, respectively).

Schroeder and Mitchener (1975b) exposed white mice of the Charles River CD strain (36-54/sex) to 0 or 5 ppm of barium (as barium acetate) in drinking water for their lifetimes. Calculated dosages based on reference values for body weight and water intake (U.S. EPA, 1988) were 1.18 mg Ba/kg-day for males and 1.20 mg Ba/kg-day for females. The diet was

characterized as a "low metal" diet and included 60% rye flour, 30% dried skim milk, 9% corn oil, 1% iodized table salt, and assorted vitamins; the barium content of the diet was not reported. Growth and body weights were not affected by the barium treatment. Histology of the heart, lung, liver, kidney, and spleen was normal. In males, longevity (defined as the mean life span of the last surviving 5 animals of each sex in each treatment group) was significantly (p=0.025) reduced at 815 days for barium-treated males as compared with 920 days for the controls. The mean life span, however, was not affected. The incidences of lymphoma leukemia and lung tumors in the male (7/37 and 4/37, respectively) and female (5/21 and 3/21) mice exposed to barium were not significantly different from the incidences in the control mice (males: 3/38 for lymphoma leukemia and 5/38 for lung tumors; females: 3/47 and 9/47, respectively).

Inhalation Studies. Inadequate. The carcinogenic potential of barium following inhalation exposure has not been adequately tested. The inhalation toxicity/carcinogenicity database is limited to a single subchronic inhalation study conducted by Tarasenko et al. (1977). This study was not designed to assess carcinogenicity; the duration was too short (4 mo) and the study design and results were poorly reported. Tarasenko et al. (1977) also conducted an intratracheal administration study. Although this single-exposure study was not designed to assess carcinogenicity, it provides some information on the progression of lesions 3, 6, and 9 months postexposure.

In the Tarasenko et al. (1977) inhalation study, male albino rats (strain and number of animals per group not reported) were exposed to 0, 1.15, or 5.2 mg/m^3 barium carbonate (0, 0.8, or 3.6 mg Ba/m^3) 4 h/day, 6 days/week for 4 mo. No information on aerosol generation or the size distribution of the particles was reported. In the introduction section of the paper, the authors state, "we have demonstrated by electron microscopy that the size of almost 80% of the dust particles is less than 2 μm"; however, it is not known if this statement refers to the aerosols generated for this study. The following endpoints were used to assess toxicity: body weight gain, arterial pressure, hematological (hemoglobin, leukocytes, and thrombocytes) and serum chemistry (glucose, phosphorus, total protein, alkaline phosphatase, and cholinesterase) parameters, urine calcium levels, bromosulfophthalein test of liver function, electrocardiogram measurement, and histological examination (tissues examined were not listed).

The authors noted that no alterations were observed in the rats exposed to 1.15 mg/m^3 barium carbonate. In the 5.2 mg/m^3 group, a number of alterations were reported; however, it does not appear that the data were statistically analyzed. The alterations included a 21% decrease in body weight gain, a 32% increase in arterial pressure, altered hematological parameters (decreases in hemoglobin and thrombocyte levels and increases in leukocyte levels), altered serum chemistry parameters (decreased sugar and total protein levels, increased phosphorus levels, decreased alkaline phosphatase activity, and increased cholinesterase activity),

increased calcium levels in the urine, impaired liver function, and histologic alterations in heart, liver, kidneys, and lungs. No alterations in the EKG readings were reported. However, when the rats were administered proserine, the EKG reading suggested disturbances in heart conductivity. The authors noted that the heart, liver, and kidneys "had a character of mild protein ('granular') dystrophy." In the lungs, the histological alterations consisted of moderate perivascular and peribronchial sclerosis with focal thickening of the intraalveolar septa and collagenation. No incidence data were provided. The presence of neoplasms was not reported; it is unclear whether the investigators looked for neoplasms. This study was not designed to assess carcinogenicity; in particular, the exposure duration was too short.

In another study conducted by Tarasenko et al. (1977), animals (species and number not specified) were administered an intratracheal dose of 50 mg barium carbonate (35 mg barium). Three months after administration, sclerotic changes were observed in the lungs. The severity of the sclerosis progressed. At 9 months, fibrous pneumonia with necrosis of mucous membranes of the large bronchi was observed. Although this study was not designed to assess carcinogenicity, the findings of the study suggested that the fibrogenic lesions progressed over time.

II.A.4. Supporting Data for Carcinogenicity

There is a limited amount of information available on the genotoxicity of barium compounds. No in vivo studies have been conducted. Most in vitro studies have found that barium chloride and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation. Ames assays with *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA97, TA98, and TA100 with or without metabolic activation (Monaco et al., 1990, 1991; NTP, 1994), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka, 1975; Kanematsu et al., 1980), and a microscreen assay with *Escherichia coli* (Rossman et al., 1991) with metabolic activation have produced negative results with barium chloride. Negative results have also been observed for barium nitrate in the rec assay using *B. subtilis* strains H17 and H45 (Kanematsu et al., 1980). Barium chloride induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation, but not in the absence of metabolic activation (NTP, 1994). Neither barium acetate nor barium chloride decreased the fidelity of DNA synthesis in avian myeloblastosis virus DNA polymerase (Sirover and Loeb, 1976). In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation (NTP, 1994).

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

Not applicable. The results of the oral carcinogenicity study suggest that barium is not likely to be carcinogenic to humans.

II.B.1. Summary of Risk Estimates

Not applicable.

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

Not applicable.

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

Not applicable.

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

Not applicable.

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

Not applicable. The inhalation database is inadequate to determine the qualitative and quantitative cancer risk for barium.

II.C.1. Summary of Risk Estimates

Not applicable.

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Not applicable.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Not applicable.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Not applicable.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2005

This assessment was peer reviewed by external scientists. Their comments have been evaluated and incorporated in finalization of this IRIS Summary. A record of these comments in included as an appendix to the Toxicological Review of Barium and Compounds (CAS No. 7440-39-3) in support of summary information on IRIS (U.S. EPA, 2005). ***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 — 2/18/1998

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Barium and Compounds conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 (email address).

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

VI. Bibliography

Barium and Compounds
CASRN — 7440-39-3

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VI.C. Carcinogenicity Assessment References

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VII. Revision History

Barium and Compounds
CASRN — 7440-39-3

Date	Section	Description
07/01/1990	I.A.	Withdrawn; new RfD verified (in preparation)
08/01/1990	I.A.	Oral RfD summary replaced; RfD changed
3/30/1998	I.A.	Oral RfD Assessment

Date	Section	Description
3/30/1998	I.B.	Inhalation RfC Assessment
3/30/1998	II.	Carcinogenicity Assessment
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
07/11/2005	I.A.	Oral RfD Assessment

VIII. Synonyms

Barium and Compounds
CASRN — 7440-39-3
Section VIII Last Revised — 07/11/2005

- 7440-39-3
- BARIUM
- UN 1399
- UN 1400
- UN 1854