2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BARIUM IN THE UNITED STATES

Barium is an alkaline earth metal, principally found as barite (barium sulfate) and witherite (barium carbonate) ores. Barium and barium compounds have a variety of uses including as getters in electronic tubes (barium alloys), rodenticide (barium carbonate), colorant in paints (barium carbonate and barium sulfate), and x-ray contrast medium (barium sulfate). Barium naturally occurs in food and groundwater. Barium concentrations in drinking water in the United States typically average 30 μg/L, but can average as high as 302 μg/L. However, individuals residing in certain regions of Kentucky, northern Illinois, New Mexico, and Pennsylvania who rely on groundwater for their source of drinking water may be exposed to barium concentrations as high as 10 times the maximum contaminant level (MCL) in drinking water of 2.0 mg/L. Low levels of barium are also found in ambient air; levels are typically less than 0.05 μg barium/m^3.

There is little quantitative information regarding the extent of barium absorption following inhalation, oral, or dermal exposure. Available evidence indicates that barium is absorbed to some extent following inhalation, oral, and dermal exposure; however, in some cases, absorption is expected to be limited. For example, there is some evidence that gastrointestinal absorption of barium in humans is <5–30% of the administered dose. The general population can be exposed to barium via inhalation, oral, or dermal exposure; under most circumstances, oral exposure would be the predominant route of exposure.

2.2 SUMMARY OF HEALTH EFFECTS

An important factor affecting the development of adverse health effects in humans is the solubility of the barium compound to which the individual is exposed. Soluble barium compounds would generally be expected to be of greater health concern than insoluble barium compounds because of their greater potential for absorption. The various barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, hydroxide) are toxic to humans. Although barium carbonate is relatively insoluble in water, it is toxic to humans because it is soluble in the gastrointestinal tract. The insoluble compounds of barium (notably sulfate) are inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans. The insoluble, nontoxic nature of barium sulfate has made it practical to use this particular barium compound in medical applications as a contrast media for x-ray examination of

the gastrointestinal tract. Barium provides an opaque contrasting medium when ingested or given by enema prior to x-ray examination. Under these routine medical situations, barium sulfate is generally safe. However, barium sulfate or other insoluble barium compounds may potentially be toxic when it is introduced into the gastrointestinal tract under conditions where there is colon cancer or perforations of the gastrointestinal tract and barium is able to enter the blood stream.

There are a number of reports of serious health effects in individuals intentionally or accidentally exposed to barium carbonate or chloride. The predominant effect is hypokalemia, which can result in ventricular tachycardia, hypertension and/or hypotension, muscle weakness, and paralysis. Barium is a competitive potassium channel antagonist that blocks the passive efflux of intracellular potassium, resulting in a shift of potassium from extracellular to intracellular compartments. The net result of this shift is a significant decrease in the potassium concentration in the blood plasma. Although the case reports did not provide information on doses, it is likely that the doses were high. In addition to the effects associated with hypokalemia, gastrointestinal effects such as vomiting, abdominal cramps, and watery diarrhea are typically reported shortly after ingestion. Similar effects have been reported in cases of individuals exposed to very high concentrations of airborne barium; the effects include electrocardiogram (ECG) abnormalities, muscle weakness and paralysis, hypokalemia, and abdominal cramps, nausea, and vomiting.

Several investigators have examined whether exposure to much lower doses of barium would adversely affect the cardiovascular system. A population-based study found significant increases in the risk of death from cardiovascular disease among residents 65 years of age and older living in communities with high levels of barium in the drinking water. However, these data cannot be used to establish a causal relationship because the study did not control for other cardiovascular risk factors or the use of water softeners, which would decrease barium levels and increase sodium levels. Two other studies did not find alterations in blood pressure and cardiac rhythm. In general, animal studies designed to assess cardiovascular function have not found significant alterations in blood pressure or ECG readings following low-dose oral exposure. One study did find significant increases in blood pressure in rats exposed to 0.80 mg barium/kg/day. However, the use of a low mineral diet with less than adequate levels of calcium may have influenced the study results.

The available animal data provide strong evidence that the most sensitive adverse effect of barium is renal toxicity. There are some reports of renal effects in case reports of individuals ingesting high doses of barium. Nephropathy has been observed in rats and mice following long-term oral exposure to barium.

In both species, there is a steep dose-response curve for the incidence of nephropathy. For example, nephropathy was not observed in mice exposed to 205 mg barium/kg/day for an intermediate duration; at 450 mg barium/kg/day, 95% of the animals exhibited mild to moderate nephropathy. Data in mice also suggest that the severity and sensitivity to renal lesions is related to duration of exposure. As noted previously, a 205 mg barium/kg/day dose is a no effect level in mice exposed to barium chloride for 90 days; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy.

The potential for barium to induce reproductive and developmental effects has not been well investigated. Decreases in the number of sperm and sperm quality and a shortened estrous cycle and morphological alterations in the ovaries were observed in rats exposed to 2.2 mg barium/m^3 and higher in air for an intermediate duration. Interpretation of these data is limited by the poor reporting of the study design and results, in particular, whether the incidence was significantly different from controls. In general, oral exposure studies have not found morphological alterations in reproductive tissues of rats or mice exposed to 180 or 450 mg barium/kg/day, respectively, as barium chloride in drinking water for an intermediate duration. Additionally, no significant alterations in reproductive performance was observed in rats or mice exposed to 200 mg barium/kg/day as barium chloride in drinking water. Decreased pup birth weight and a nonsignificant decrease in litter size have been observed in the offspring of rats exposed to 180/200 mg barium/kg/day as barium chloride in drinking water prior to mating.

Several studies have examined the carcinogenic potential of barium following oral exposure and did not find significant increases in the tumor incidence. No studies have adequately assessed the carcinogenicity of barium following inhalation exposure. The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not assessed the carcinogenicity of barium. The EPA has concluded that barium is not classifiable as to human carcinogenicity, Group D. However, under EPA's revised guidelines for carcinogen risk assessment, barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for barium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive

health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for barium because studies evaluating the effects of barium in humans and animals following acute, intermediate, and chronic inhalation exposure were inadequate for establishing the exposure concentrations associated with adverse health effects. Five reports of occupational exposure to barium have been identified. In one study (Doig 1976), a benign pneumoconiosis was observed in several workers exposed to barium sulfate; two other studies did not find barium-related alterations in the respiratory tract of workers exposed to barium sulfate (Seaton et al. 1986) or barium carbonate (Essing et al. 1976). Other effects reported in the occupational exposure studies were an increase in blood pressure (Essing et al. 1976), gastrointestinal distress, muscle weakness and paralysis, absence of deep tendon reflex, and decreased serum potassium levels in a worker exposed to barium carbonate powder (Shankle and Keane 1988). A fifth study did not find alterations in plasma potassium levels in welders using barium-containing electrodes (Zschiesche et al. 1992). Interpretation of these studies is limited by the small number of subjects, possible lack of a control group, and/or the lack of quantitative exposure information.

Three animal studies evaluating the toxicity of inhaled barium have also been identified. Two of the studies reported adverse respiratory tract effects including lung lesions (perivascular and peribronchial sclerosis and focal thickening of the intraalveolar septa) in rats exposed to 3.6 mg barium/m^3 as barium carbonate dust 4 hours/day, 6 days/week for 4 months (Tarasenko et al. 1977) and bronchoconstriction in guinea pigs exposed to 0.06 mg barium/m^3/minute as barium chloride for an unspecified amount of time

(Hicks et al. 1986). The third study (Cullen et al. 2000) did not find histological alterations in the lungs of rats exposed to 44.1 mg barium/m^3 as barium sulfate for 7 hours/day, 5 days/week for 119 days. Increases in blood pressure were observed in the Tarasenko et al. (1977) and Hicks et al. (1986) studies. Tarasenko et al. (1977) also reported hematological, reproductive, and developmental effects in rats exposed to barium carbonate dust. None of these studies provide a suitable basis for an inhalation MRL. The Tarasenko et al. (1977) studies are limited by poor reporting of the study design and results, lack of incidence data, and lack of statistical analysis for many of the end points. The Hicks et al. (1986) study did not report the frequency or length of exposure, the number of animals used was not clearly reported, and it does not appear that control animals were used. Although the Cullen et al. (2000) study was well reported and designed, it only examined the respiratory tract and did not identify an adverse effect level. Oral exposure studies identify the kidney as the most sensitive target of toxicity; this end point was not evaluated in the Cullen et al. (2000) study.

Oral MRLs

There are numerous case reports of individuals intentionally or accidentally ingesting unreported but presumably high doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Silva 2003; Talwar and Sharma 1979; Wetherill et al. 1981). The consistently observed effects included abdominal distress (vomiting, abdominal cramping, and watery diarrhea), numbness around the face, muscle weakness, paralysis, and ventricular tachycardia.

Information on the acute oral toxicity of barium is limited to two studies in rats conducted by Borzelleca et al. (1988). A nonsignificant increase in mortality (3/20 females compared to 0/20 in controls) was found in rats receiving gavage doses of 198 mg barium/kg/day as barium chloride in water for 10 days. In the other study conducted by this group, 15/20 animals died after a single dose of 198 mg barium/kg/day as barium chloride in water. In the 10-day study, significant decreases in relative kidney weight (kidney:brain ratio) were observed in female rats administered 66–138 mg barium/kg/day and decreases in blood urea nitrogen (BUN) levels were observed in female rats dosed with 66–198 mg barium/kg/day and male rats dosed with 198 mg barium/kg/day. The magnitude of change in BUN levels was small (less than 15%) and was not dose-related; the decrease in BUN was not considered to be biologically significant. Additionally, BUN levels are typically increased in response to kidney damage. Significant decreases in absolute ovary weight and relative ovary weight (ovary:brain ratio) were observed at 198 mg barium/kg/day in the 10-day study. The biological significance of this change in organ weight is

questionable; no gross alterations in the ovaries were observed in this study and no histological alterations were observed in rats or mice exposed to barium chloride for acute, intermediate, or chronic durations to barium doses as high as 180 mg barium/kg/day in rats (NTP 1994) and 495 mg barium/kg/day in mice (NTP 1994).

The data are considered inadequate for derivation of an acute-duration oral MRL for barium. The available animal studies (Borzelleca et al. 1988) have evaluated the toxicity of barium chloride in repeated dose studies; however, neither study identified a non-lethal biologically significant adverse effect level. Longer-term studies identify the kidney as the most sensitive target; however, it is not known if the kidney would also be the most sensitive target following acute-duration exposure. Data in mice suggest that the severity and sensitivity to renal lesions are related to duration of exposure. The intermediate-duration mouse study identified a NOAEL of 205 mg barium/kg/day; however; a 2-year exposure to 200 mg barium/kg/day resulted in moderate to marked nephropathy (NTP 1994). Derivation of an MRL using the highest identified no-observed-adverse-effect level (NOAEL) is not recommended at this time because critical targets of toxicity and dose-response relationships have not been established for this exposure category. The exposure levels are poorly characterized in the available reports of human poisonings, acute-duration animal studies have failed to identify the critical target of barium toxicity, and it is possible that the critical target (kidneys) following long-term exposure may not be a sensitive target following short-term exposure.

- An MRL of 0.2 mg barium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to barium.

Information on the oral toxicity of barium in humans following intermediate-duration oral exposure is limited to an experimental study in which men were exposed to 0.1 or 0.2 mg barium/kg/day as barium chloride in drinking water for 4 weeks (Wones et al. 1990). No significant alterations in blood pressure or ECG readings, relative to initial baseline measurements, were found.

A number of animal studies have evaluated barium toxicity following intermediate-duration oral exposure. Several of these studies focused on the cardiovascular system or assessed cardiovascular function. Perry et al. (1983, 1985, 1989) reported significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. NTP (1994) and McCauley et al. (1985) did not find significant alterations in blood pressure or ECG readings in rats exposed to 150 or 180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989)

studies and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies influenced the results. The calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of the McCauley et al. (1985) and NTP (1994) studies suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. In the NTP (1994) 13-week rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, the difference between motor activity in the barium-exposed rats and the controls was less than 20% and was not considered to be biologically significant. At 180 mg barium/kg/day, the difference was 30% in the female rats, which was considered to be adverse. No significant alterations were found on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure of male and female rats to 180/200 mg barium/kg/day resulted in decreased pup birth weight and a nonsignificant decrease in litter size; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental

effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992). Another study (Tarasenko et al. 1977) also reported developmental effects (increased offspring mortality during the first 2 months and disturbances in liver function) in an unspecified animal species; however, the lack of information on experimental methods, exposure conditions, and results limits the usefulness of this study for evaluating the potential of aluminum to induce developmental toxicity.

Based on these data, the kidney appears to be the most sensitive target following intermediate-duration oral exposure to barium. Three studies identified adverse effect levels for kidney effects: (1) a lowest-observed-adverse-effect level (LOAEL) of 150 mg barium/kg/day was identified in uninephrectomized and salt-sensitive and salt resistant rats (McCauley et al. 1985), (2) a LOAEL of 115 mg barium/kg/day was identified for increased kidney weight in rats; the NOAEL was 65 mg barium/kg/day (NTP 1994), and (3) a LOAEL of 450 mg barium/kg/day for nephropathy in mice; the NOAEL was 205 mg barium/kg/day (NTP 1994). The NTP (1994) 13-week rat study, which identified the lowest LOAEL for a kidney effect, was selected as the basis of the intermediate-duration oral MRL; the change in kidney weight was considered an early indicator of potentially more serious effects in the kidney.

In this study (NTP 1994), groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate (0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females) in drinking water for 90 days. Exposure-related deaths were observed during the last week of the study in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day; an increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. Minimal to mild, focal to multifocal dilatation of the proximal renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed

to 75 mg barium/kg/day for 2 years (NTP 1994). Thus, this study identifies a NOAEL of 65 mg barium/kg/day and a LOAEL of 115 mg barium/kg/day.

A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data. Thus, the intermediate-duration oral MRL of 0.2 mg barium/kg/day was calculated by dividing the NOAEL of 65 mg barium/kg/day by an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

- An MRL of 0.2 mg barium/kg/day has been derived for chronic-duration oral exposure (>365 days) to barium.

Several human and animal studies have examined the toxicity of barium following chronic-duration exposure. Two community-based studies have evaluated the possible association between elevated levels of barium in drinking water and increased risk of cardiovascular disease. No significant alterations in blood pressure measurements or increases in the prevalence of hypertension, heart disease, or stroke were found among residents of two communities with elevated (0.2 mg barium/kg/day) or low (0.003 mg barium/kg/day) levels of barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). In the second study, significantly higher mortality rates, particularly among individuals 65 years of age and older, for cardiovascular disease and heart disease (arteriosclerosis) were found in a community with elevated barium drinking water levels (0.06–0.3 mg barium/kg/day) as compared to a community with low barium levels (0.006 mg barium/kg/day) (Brenniman and Levy 1985; Brenniman et

al. 1979a, 1981). A common limitation of both studies is the lack of information on tap water consumption, actual barium intakes, and duration of exposure. Additionally, the second study did not control for a number of potential confounding variables, particularly the use of water softeners, which would have resulted in a decrease in barium levels in the drinking water and an increase in sodium levels.

Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet, which may have supplied inadequate levels of calcium. No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality (NTP 1994).

As with intermediate-duration exposure, the animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 1994). The chronic-duration mouse study (NTP 1994) was selected as the basis of the chronic-duration MRL for barium.

In this study (NTP 1994), groups of 60 male and 60 female B6C3F1 mice were exposed to 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate (0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females) in drinking water for 2 years. Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was

observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group.

A benchmark analysis of the incidence data for nephropathy in mice was conducted; details of this analysis are presented in Appendix A. A benchmark dose (BMD) of 80.06 mg barium/kg/day, which corresponds to a 5% increase in the incidence of nephropathy was calculated; the 95% lower confidence limit on the BMD (BMDL) was 61.13 mg barium/kg/day. The $BMDL_{05}$ was selected as the point of departure for deriving the chronic-duration oral MRL. The dose corresponding to a predicted 5% incidence was selected over the typically 10% incidence as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality. Thus, the chronic-duration oral MRL of 0.2 mg barium/kg/day is based on the $BMDL_{05}$ of 61 mg barium/kg/day in male mice and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability) and a modifying factor of 3. The modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.