PRIORITY DATA NEEDS FOR BARIUM

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NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR Decision guide for identifying substance-specific data needs related to toxicological profiles (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

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I. Executive Summary

Barium is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA) (ATSDR 2008a, 2008b). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) the potential for human exposure to the substance. An updated Toxicological Profile for Barium was published by ATSDR in August 2007.

Metallic barium is a silvery-white soft metal, but takes on a silver-yellow color when exposed to air. Like other alkaline earth metals, barium decomposes in water, evolving hydrogen gas. Barium oxidizes readily in moist air. In powdered form, barium reacts violently with air. Because of its high reactivity, barium does not exist as the metal in the environment; it exists in a combined state with other elements. Because of their commercial importance and risk of human exposures, eight barium compounds are also covered in the toxicology profile: barium acetate, barium carbonate, barium chloride, barium cyanide, barium hydroxide, barium oxide, barium sulfate, and barium sulfide. Barium acetate, barium chloride, barium cyanide, barium hydroxide, and barium oxide are quite soluble in water. Barium carbonate and sulfate are poorly soluble in water. Barium oxide reacts rapidly with carbon dioxide in water to form barium hydroxide and barium carbonate. Barium sulfide slowly decomposes in water, forming barium hydroxide, barium salts of hydrosulfide and other oxidized sulfur species, and elemental sulfur.

Barium is obtained through the mining of crude barite ore, which contains mostly barium sulfate. In 2003, there were six mines in three states, Georgia, Nevada, and Tennessee, producing crude barite at a volume of 550,000 metric tons. The United States also imported 1,620,000 metric tons

of crude barite in 2003. In the United States, the crude barite is further processed by 26 mills and grinders into 2,500,000 metric tons of ground or crushed barite. The predominant use of the ground or crushed barite (94% in 2003) is in well drilling operations to both lubricate the drilling bit and seal the well against the pressurized gases within the well. The barium sulfate in the remaining 6% of ground barite is further refined and used as a colorant in high-quality paints, in glass and paper manufacturing, as a filler in plastics, rubber, and brake linings, as an additive in concrete to increase radiation shielding, as a benign, radiopaque aid in x-ray diagnosis, and in the production of other barium compounds. It is also used to produce barium sulfide, which is the starting point for the production of most of the other barium compounds.

Barium's production and use will result in its release to the environment, with emissions occurring largely to soils. In soil, the mobility of barium is determined by the properties of the soil, including cation exchange capacity, calcium carbonate content, and pH. Barium mobility is limited in soils with high cation exchange capacity and high calcium carbonate content. Barium is more mobile in soils with high chloride content and/or lower pHs. When released into air, barium is likely to be present in particulate form with removal from air largely occurring through dry and wet deposition. The residence time in air may be several days, depending on the size of the particulate, the chemical nature of the particulate, and environmental factors such as rainfall. In water, barium is expected to mostly precipitate out of solution as the insoluble salts, barium sulfate and barium carbonate. The solubility of barium is dependent on pH and the concentration of various anions (e.g. carbonate, chloride, and sulfate). Sedimentation of suspended solids removes a large portion of barium from surface waters as the insoluble sulfate salt.

The general population is exposed to barium primarily through the diet and, to a much lesser extent, through inhalation of particulates containing barium. Occupational exposures to barium occur through inhalation and dermal contact in the workplace where it is produced or used. Populations residing near waste disposal sites may be subject to higher than average levels of barium in drinking water obtained from groundwater wells due to the possibility of barium leaching into groundwater, especially near landfills. These populations may also be exposed to higher than average levels of barium in air since barium could be carried in particulates emitted to air through wind or anthropogenic activities. Children are expected to be exposed to barium by the same route as adults. The primary route of exposure for children is through the diet. Children who live near hazardous waste sites or municipal landfills may be subject to higher levels of

barium in drinking water obtained from groundwater wells and in air. The use of contaminated drinking water for bathing may result in dermal exposures to barium.

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. The insoluble compounds of barium (notably sulfate) are inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans following ingestion.

There are a number of reports of serious health effects in individuals ingesting barium carbonate or chloride or inhaling airborne barium; most of these case reports did not provide exposure information, but it is likely that the doses were high. These studies suggest that high-dose exposure results in hypokalemia, cardiovascular effects, neuromuscular effects, and gastrointestinal upset. Epidemiology studies of populations exposed to elevated barium levels in drinking water or human experimental studies failed to identify critical targets of long-term toxicity. The available animal data provide strong evidence that the most sensitive adverse effect of barium is renal toxicity. Oral carcinogenicity studies in rats and mice provide suggestive evidence that barium is not carcinogenic following oral exposure. The available data are inadequate to evaluate whether barium would be carcinogenic following inhalation or dermal exposure. There is also some information that the developing organism may also be a target of toxicity (decreases in pup body weight have been observed). There are implications, based on research in young experimental animals, that children may absorb more barium through the gastrointestinal tract than adults; there are no data to evaluate whether children would be more susceptible to barium toxicity.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- No exposure priority data needs have been identified.

Toxicity

- Dose-response data for acute-duration via oral exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium and barium compounds are available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;
- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;
- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information to improve the database to conduct public health assessments.

This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for barium occurred when the data needs for barium were determined in the ATSDR Toxicological Profile for barium. Considered a subset of all information gaps on barium, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for barium were addressed before the toxicological profile was finalized. In preparing the priority data needs document, a literature search was conducted to provide updated information on barium.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for barium and subject them to further scientific evaluation. This will lead to priorities and

ultimately to ATSDR's substance-specific research agenda. To affect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not the same priority.
- Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned multigenerational animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.
- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

- Development and/or confirmation of appropriate analytical methods.
- Determination of environmental and human exposure levels when analytical methods are available.
- Bioavailability studies for substances of known significant toxicity and exposure.
- Studies available to characterize target organs and dose response.

- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.
- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

1. Frequency of Occurrence

Finding: Barium is included in the priority list of hazardous substances identified by ATSDR and EPA (ATSDR 2008a, 2008b).

Barium has been detected in at least 798 of 1,684 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to barium at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

Finding: ATSDR scientists have determined that there has been considerable past human exposure and that the potential exists for current human exposure to barium via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to barium. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for Barium, Chapter 6, on Potential for Human Exposure (ATSDR 2007).

Metallic barium is a silvery-white soft metal, but takes on a silver-yellow color when exposed to air (Boffito 2002; Genter 2001). Like other alkaline earth metals, barium decomposes in water, evolving hydrogen gas. Barium oxidizes readily in moist air. In powdered form, barium reacts violently with air. Because of its high reactivity, barium does not exist as the metal in the environment; it exists in a combined state with other elements. Because of their commercial importance, eight barium compounds are covered in the toxicology profile: barium acetate, barium carbonate, barium chloride, barium cyanide, barium hydroxide, barium oxide, barium sulfate, and barium sulfide. Barium acetate, barium chloride, barium cyanide, barium hydroxide, and barium oxide are quite soluble in water. Barium carbonate and sulfate are poorly soluble in water. Barium oxide reacts rapidly with carbon dioxide in water to form barium hydroxide and barium carbonate (Dibello et al. 2003). Barium sulfide slowly decomposes in water, forming barium hydroxide and barium hydrosulfide. Barium sulfide is also known to undergo slow oxidation in solution to form elemental sulfur and various oxidized sulfur species including the sulfite, thiosulfate, polythionates, and sulfate. The water solubility of barium compounds increases with decreasing pH (IPCS 1991).

Barium is obtained through the mining of crude barite ore, which contains mostly barium sulfate. The predominant use of barite ore (94% in 2003) is in well drilling operations to both lubricate the drilling bit and seal the well against the pressurized gases within the well (USGS 2005). Refined barite produces the *blanc fixe* form of barium sulfate that is used in high-quality paints, in glass and paper manufacturing, as a filler in plastics, rubber, and brake linings, and in the production of other barium compounds (Dibello et al. 2003). Barium sulfate is also added to concrete to increase the radiation shielding of the material. Chemically pure barium sulfate is used as a benign, radiopaque aid to x-ray diagnosis in colorectal cancer and some upper

gastrointestinal examinations (de Zwart et al. 2001; Doull et al. 1980; ILO 1983; Lin 1996; Newman 1998; Pijl et al. 2002; Rae 1977). Barium sulfide is produced from barium sulfate and is the starting point for the production of most of the other barium compounds (Dibello et al. 2003; ILO 1983). Barium carbonate, chloride, and hydroxide play an important role in the brick, tile, ceramic, photographic, and chemical manufacturing industries (Bodek et al. 1988; Dibello et al. 2003). Barium carbonate has also been used as a rodenticide (Meister 2004; Worthing 1987). Barium oxide is used to dry gases and solvents, to strengthen ceramics, and as a component in some specialty cements (Dibello et al. 2003). Barium hydroxide plays a role in glass manufacturing, synthetic rubber vulcanization, in the production of barium greases and plasticizers, as a component in sealants, pigment dispersion, paper manufacturing, sugar refining, in animal and vegetable oil refining, and in the protection of objects made of limestone from deterioration. Barium acetate is used in printing fabrics, in lubricating grease, and as a catalyst for organic reactions. Barium metal and alloys are used as "getters" in vacuum and picture tubes to remove residual gases.

Barium and barium compounds are important substances for research because of their widespread environmental contamination. According to the Toxic Chemical Release Inventory (TRI), 100 facilities manufactured or processed barium and 1,007 facilities manufactured or processed barium compounds in 2004 (TRI04 2006). It was estimated that 216 million pounds of barium and barium compounds, amounting to 93.7% of the total environmental release, were discharged to land from manufacturing and processing facilities in the United States in 2004 (TRI04 2006). Much smaller amounts, 2.51 and 1.48 million pounds, were released to air and water, respectively, in addition to 0.023 million pounds injected underground (TRI04 2006). The TRI data should be used with caution because only certain types of facilities are required to report. Natural sources of barium release are the weathering of rock and minerals. Releases of this compound to the environment due to anthropogenic activities may result from the manufacture, use, storage, distribution, and disposal of barium and barium compounds. The major anthropogenic releases of these compounds to the environment are to land from disposal of drilling fluids and muds by land farming (Bates 1988). Emissions of barium into air occur as the result of the release of fugitive dust and particulate matter during the mining, refining, and production of barium and barium compounds (Miner 1969). Davis (1972) estimated the percentage of total barium release from various sources in 1969 as 18% from the processing of barite ore, 28% from the production of barium compounds, 23% from the manufacture of various end products (e.g., drilling well muds, and glass, paint, and rubber products), and 26% from the

combustion of coal. Barium that is found in surface water and groundwater is predominantly obtained from natural sources. However, barium concentrations in marine water will likely be higher than natural background concentrations near off-shore drilling platforms as a result of the discharge of drilling muds, cuttings, and produced water containing barium from these facilities (Ng and Patterson 1982).

Barium is not expected to distribute widely upon release to air, water, or soil. When released into air, barium is likely to be present in particulate form with removal from air largely occurring through dry and wet deposition (EPA 1984). The residence time in air may be several days, depending on the size of the particulate, the chemical nature of the particulate, and environmental factors such as rainfall (EPA 1984; WHO 2001). In water, barium is expected to precipitate out of solution as insoluble salts (e.g., barium sulfate and barium carbonate). At pH levels of 9.3 or below, the formation of barium sulfate limits the barium concentration in natural waters (Bodek et al. 1988). The presence of chloride (Cl^-) and other anions (e.g., nitrate [NO_3^-] and carbonate [CO_3^-]) increases the solubility of barium sulfate at pH 9.3 or below. At pH >9.3 in the presence of carbonate, barium carbonate becomes the dominant species in natural waters (Bodek et al. 1988; Singer 1974). Due to its very low solubility and fast precipitation kinetics, barium carbonate limits the soluble barium concentration under alkaline conditions (Faust and Aly 1981; Hem 1959; Rai et al. 1984; Singer 1974). Sedimentation of suspended solids removes a large portion of barium from surface waters (Benes et al. 1983). Barium in sediments is found largely as barium sulfate (González-Muñoz et al. 2003). The precipitation of barium as barium sulfate is especially accelerated at the point where rivers empty into the ocean due to the high sulfate content (905 mg/L) of ocean water (Bowen 1966). In soil, the mobility of barium is determined by the properties of the soil, including cation exchange capacity, calcium carbonate content, and pH (WHO 2001). Barium mobility is limited in soils with high cation exchange capacity (e.g., fine textured mineral soils and soils containing a high amount of organic matter) and high calcium carbonate content (Bates 1988; Kabata-Pendias and Pendias 1984; Lagas et al. 1984). Barium binds to soil either through reactions with metal oxides (e.g., Al_2O_3, MnO_2, SiO_2, and TiO_2) and hydroxides or through electrostatic interactions (Bodek et al. 1988; Hem 1959; Rai et al. 1984; Singer 1974). Barium is strongly absorbed by clay minerals (Bodek et al. 1988). Barium is more mobile in soils with high chloride content or lower pHs (Bates 1988; Lagas et al. 1984; WHO 2001). In soils affected by acidic landfill leachate, barium will be much more mobile due to the formation of complexes with fatty acids present in leachate (Lagas et al. 1984).

Barium and barium compounds have been identified in at least 798 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for barium and barium compounds is not known. Barium has been identified in air samples collected at 24 sites, surface water samples collected at 257 sites, groundwater samples collected at 561 sites, soil samples collected at 369 sites and sediment samples collected at 260 of the 798 NPL hazardous waste sites was detected in some environmental media (HazDat 2006).

The general population is exposed to barium through the consumption of food and water and inhalation of ambient air (ICRP 1974; Reeves 1979; WHO 2001). The concentration of barium in ambient air within the United States is generally <0.05 μg/m^3 (IPCS 1991) with an average concentration in urban atmospheres of 0.012 μg/m^3 (Bowen 1979). The concentration of barium in ambient air sampled within urban and suburban atmospheres ranged between 0.0015 and 0.95 μg/m^3 (EPA 1984). Based on this range of barium concentrations in air and assuming an inhalation volume for an average adult of 20 m^3/day (EPA 1989), the intake of barium through inhalation would range from 0.03 to 19 μg barium/day. For individuals living near a barium emission point, such as a barium production or processing plant, the exposure to barium in air is expected to be greater than for the general population. Using an average population density of 27 persons/km^2 (based on actual population data from areas surrounding barium production and processing plants), it has been estimated that approximately 0–886 persons within an area of up to 32.8 km^2 around a source site could be exposed to soluble barium compound concentrations of >1.67 μg/m^3 in ambient air (Reznik and Toy 1978). Assuming that the average adult daily ventilation rate is 20 m^3, breathing these ambient air barium concentrations would result in daily respiratory intakes of >32 μg. No other correlations have been established between barium concentrations in air and geographical areas or land-use types.

Barium concentrations in most drinking water in the United States are <200 μg/L with an average concentration of 30 μg/L (EPA 2005; Thomas et al. 1999). Using the average concentration of 30 μg/L for the barium in drinking water, it is estimated that the average daily intake of barium in drinking water for an adult in the United States is 60 μg (0.86 μg/kg body weight/day for a 70-kg adult), assuming a drinking water volume of 2 L/day. There are regions in the United States (e.g., Illinois, Kentucky, Pennsylvania, and New Mexico) where barium concentrations in groundwater that is used as drinking water are up to 10 times higher than the maximum concentration limit (MCL) value of 2,000 μg/L (Calabrese 1977; EPA 2005). The elevated barium concentrations in

groundwater within these regions are likely the result of leaching and erosion of barium from sedimentary rock (Calabrese 1977; Kojola et al. 1978).

Representative data on barium intake through the diet for residents of the United States are available from a study of four individuals. It is estimated that the daily barium intake ranges of 650–1,770 µg/day, or 9.30–25.3 µg/kg body weight/day based on an adult body weight of 70 kg (Tipton et al. 1966, 1969). Data from a recent total diet study conducted in Canada (1993–1999) shows daily barium intakes from the diet to average 8.817 µg/kg body weight/day with intake dependent on age, sex, and ethnicity (Health Canada 2005). Populations residing near waste disposal sites may be subject to higher than average levels of barium in drinking water that is obtained from groundwater at sites were barium is expected to be mobile, such as sites where the soil pH is low or at landfills with acidic leachate. Exposure to barium in air may also be a problem at sites where dust is produced through the disturbance of soil by wind or anthropogenic activities. However, data of exposures of residents living near hazardous waste sites through inhalation of air or ingestion of drinking water could not be located.

Children are exposed to barium predominantly through food and drinking water and, to a much lesser extent, through the inhalation of barium in air. From the Canadian Total Diet Study (1993–1999), it was shown that the average daily barium intake of barium is highest for children aged 0–4 years of age, with values increasing from 20.760 µg/kg body weight/day for infants (0–1 months) to 25.251 µg/kg body weight/day for children 1–4 years of age (Health Canada 2005). For children in the age groups 5–11 and 12–19 years, the average daily barium intake continually decreases to values of 18.741 and 11.759 µg/kg body weight/day, respectively, for males and 18.741 and 9.280 µg/kg body weight/day, respectively, for females. For children in the United States, it is estimated that barium intake through the consumption of drinking water ranges from 36 to 60 µg/day, based on an average concentration of barium in drinking water of 30 µg/L (Thomas et al. 1999) and the consumption of 1.2–2.0 L of drinking water per day. Data on intake of barium through exposure to barium in air was not available for children. However, the intake of airborne barium by children in the general population and those living near hazardous waste sites to airborne barium is expected to be very minor in comparison to the intake of barium through the diet.

Occupational exposure to barium may occur through inhalation and dermal contact at workplaces where this compound is produced or used. Data from a workplace survey conducted by NIOSH

from 1980 to 1983 are summarized in the following table, including the numbers of workers (female workers) and facilities in the United States that are occupationally exposed to barium and barium compounds (NIOSH 1989; RTECS 2004).

Number of Workers Potentially Exposed to Barium and Barium Compounds

Chemical	Number of plants	Total workers (female workers)
Barium	815	10,308 (3,598)
Barium carbonate	4,494	61,019 (6,889)
Barium chloride	4,293	57,767 (15,249)
Barium hydroxide	1,423	35,351 (12,208)
Barium oxide (BaO_2)	46	511 (325)
Barium nitrate	353	9,625 (2,699)
Barium sulfate	20,089	305,887 (83,800)
Barium sulfide	7	7 (0)
Chromic acid (H_2CrO_4), barium salt (1:1)	20	3,546 (1,984)

Source: NIOSH 1989

3. Toxicity

Finding: ATSDR considers that short, intermediate, and long-term health effects can result from oral contact of barium. Target organs or systems known to be affected include kidneys, neuromuscular system, gastrointestinal tract, and possibly the developing organism.

The following is a brief summary of the toxicology of barium. Refer to the ATSDR Toxicological Profile for Barium chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2007).

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. The insoluble compounds of barium (notably sulfate) are inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans (ILO 1983). There are a number of reports of serious health effects in individuals intentionally or accidentally exposed to barium carbonate or chloride (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Talwar and Sharma 1979; Wetherill et al. 1981). The predominant effect is hypokalemia (below normal levels of potassium in the blood), which can result in ventricular tachycardia, hypertension and/or hypotension, muscle weakness, and paralysis. In addition, 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 (Essing et al. 1976), muscle weakness and paralysis (Shankle and Keane 1988), hypokalemia (Shankle and Keane 1988), and abdominal cramps, nausea, and vomiting (Shankle and Keane 1988).

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 (Lewi and Bar-Khayim 1964; McNally 1925; Phelan et al. 1984; Wetherill et al. 1981). Nephropathy has been observed in rats and mice following long-term oral exposure to barium (McCauley et al. 1985; NTP 1994). 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 (NTP 1994). 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. 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 (NTP 1994). 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 (Dietz et al. 1992). Decreased body weight and a non-significant decrease in litter size have been observed in the offspring of rats

exposed to 180 mg barium/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992).

Several studies have examined the carcinogenic potential of barium following oral exposure (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b) 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 classified barium as to its carcinogenicity. The EPA has concluded that barium is not classifiable as to human carcinogenicity, Group D (IRIS 2005). 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 (IRIS 2005).

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for barium, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

- Development and/or confirmation of appropriate analytical method;
- Determination of environmental and human exposure levels when analytical methods are available; and
- Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

Barium metal is unstable in the environment and therefore barium exists in the +2 oxidation state mainly as the sulfate or carbonate salts. Also, there are a number of commercially important barium compounds that have the potential to be released to the environment or human exposure. Therefore, this priority data needs document addresses both barium metal and the barium compounds, barium acetate, barium carbonate, barium chloride, barium cyanide, barium hydroxide, barium oxide, barium sulfate, and barium sulfide, as one group.

1. Levels I & II Data Needs

a. Analytical Methods

***Purpose*:** To determine if available methods are adequate to detect and quantify levels of barium in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

***Finding*:** A data need has not been identified. Analytical methods exist for the detection of barium in human biological samples and environmental media. These methods are sufficiently sensitive and reliable enough to measure background levels in the general population as well as levels at which health effects might occur after short-term or long-term exposure.

Analytical methods for determining barium in biological samples are available and involve the detection of the barium ion or barium as the sulfate salt. Atomic emission spectroscopy (AES) using either inductively-coupled plasma (ICP) or electric arc as the excitation source is the common methods for measuring barium in biological media. Methods exist for the detection of barium in urine (Mauras and Allain 1979; Schramel 1988), blood and plasma (Mauras and Allain 1979; Olehy et al. 1966), bone (Shiraishi et al. 1987), and tissues (Baisane et al. 1979; Borchardt et al. 1961). Detection sensitivities for barium in urine are at or close to 0.2 μg/L. Data on recoveries are not available, but a low coefficient of variation of 3–7% was reported by Mauras

and Allain (1979) for their barium urinalysis assay. The detection limits for barium in blood, plasma, and erythrocytes are 0.6, 66, and 7 μg/L, respectively (Mauras and Allain 1979; Olehy et al. 1966). Recovery data were not available, but relative standard deviations (RSDs) of 7.6 and 28.5% were reported for the analysis of barium in plasma and erythrocytes, respectively. In bone, detection limits for barium were 0.0005 μg/g with a RSD value of 0.5% (Shiraishi et al. 1987). Detection sensitivities and recoveries were not available for the analysis of barium in visceral tissues by gravitimetric techniques, but recoveries of 86.8–130.5% were reported for an AES technique (Baisane et al. 1979; Borchardt et al. 1961).

Commonly used methods for detecting barium in environmental samples are flame atomic absorption spectroscopy (FAAS) and graphite furnace atomic absorption spectroscopy (GFAAS). However, inductively-coupled plasma-atomic emission spectroscopy (ICP-AES) and ICP-mass spectrometry (ICP-MS) techniques are becoming more commonly used, especially for conducting trace metal analyses in complex environmental media. Methods exist for measuring the concentration of barium in air (NIOSH 1994, 2003), water (ASTM 2000; Edelbeck and West 1970; EPA 1974, 1994a, 1994b; Fagioli et al. 1988; Johnson et al. 1983; Pierce and Brown 1977; Roe and Froelich 1984), soil (EPA 1978, 1996; USGS 2002a, 2002b), sediment (USGS 2002a, 2002b), and rocks and minerals (Bano 1973; USGS 2002a, 2002b). The greatest source of human exposure to barium in the general population in the United States is consumption of food that contains barium. A standard method used in the National Human Exposure Assessment Survey (NHEXAS) for measuring barium in food and beverages used microwave digestion to prepare samples for analysis by ICP-AES (EPA 1995b). Detection sensitivities and recoveries were 0.03 mg/kg and 86–94%, respectively, in food and 0.004 mg/kg and 86–92%, respectively, in beverages. Other potential routes of human exposure include ingestion of drinking water and, to a much lesser extent, inhalation of particulate matter containing barium. Barium can be measured in the sub-ppb to ppb in air and water for most assays, with recoveries generally >75%. Methods for measuring barium in soils and sediment range are capable of detection sensitivities of 0.15–0.3 ppm and provide good recoveries ranging from 96 to 106%. The sensitivity of the methods for detecting barium in air, water, and food/beverages are sufficient for detecting levels of the compound that may be of human health concern.

***Priority Recommendation*:** A data need has not been identified.

b. Physical/Chemical Properties

***Purpose*:** To determine whether adequate data on the chemical and physical properties of barium are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

***Finding*:** A data need has been identified. The relevant physical and chemical properties of barium metal and eight barium compounds (barium acetate, barium carbonate, barium chloride, barium cyanide, barium hydroxide, barium oxide, barium sulfate, and barium sulfide) including solubility in water (Budavari et al. 2001; Dibello et al. 2003; Lide 2000; Stokinger 1981; Weast 1989) and organic solvents (Budavari et al. 2001; Weast 1989), vapor pressures (Boffito 2002; Dibello et al. 2003; NIOSH/OSHA 1978; Preisman and Davis 1948), and reactivities (Budavari et al. 2001; DOT 2004; HSDB 2005; Lewis 2000) have been measured experimentally or have been estimated accurately enough for the inorganic barium compounds to permit evaluating the environmental fate and transport of barium. Limited data are available on the physical and environmental fate properties of the organic barium compounds, such as barium acetate and barium cyanide. Additional studies on the partitioning of organic barium compounds between soil and water in different soils types may be useful for understanding the mobility of these compounds through soil, particularly for hazardous waste sites where the concentrations of organic contaminants are likely to be high and the incidence for increased mobility of barium through soils is likely.

***Priority Recommendation*:** The identified data need for studies on the partitioning of the organic barium compounds, barium acetate and barium cyanide, between soil and water in different soil types is not a priority. This information is useful for understanding the potential for increased mobility of organic barium compounds in soils at hazardous waste sites where the levels of organic contaminants coupled with lower pH of leachates or soils. However, the information gained from these studies is expected to be specific for barium acetate and barium cyanide and it is not likely that the data obtained from the testing of these two compounds will adequately represent the partitioning of more common forms of organic barium (e.g., barium compounds with fatty acids) that are likely to be found at these sites.

c. Exposure Levels

(1) Environmental Media

***Purpose*:** To determine whether adequate data are available on the levels of barium in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A data need to obtain reliable and current data on concentrations of barium in contaminated environmental media at hazardous waste sites has been identified.

The concentrations of barium in ambient air are estimated to be <0.05 μg/m^3 (IPCS 1991). In a study of 18 cities in the United States, the concentrations of barium in ambient air ranged from <0.005 to 1.5 μg/m^3 (Tabor and Warren 1958). A distinct pattern between barium concentrations in air and the extent of industrialization was not observed in this study. A similar range of barium concentrations in air, 0.0015–0.95 μg/m^3, to that reported by Tabor and Warren was obtained in another study of ambient air in the United States (EPA 1984; WHO 2001). Concentrations of barium in particulate matter emitted from a barium processing facility and sampled at sites along the plant boundaries were higher (1.3–330 μg/m^3) than the ambient concentrations given above (Reznik and Toy 1978). In a sampling of 49 Canadian residences, the barium concentrations in indoor dust was found to average 405.56 mg barium/kg dust with a median value of 222.22 mg barium/kg dust (Butte and Heinzow 2002; Rasmussen et al. 2001). Populations residing near hazardous waste sites may be subject to above average levels of barium in the ambient air. Barium has been detected in air samples collected at 24 of the 798 hazardous waste sites where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of barium in outdoor air were 0.015–170 and 0.0135–639 μg/m^3 in onsite and offsite sampling, respectively (HazDat 2006).

Barium is found in raw surface water and drinking water with a high frequency of detection (99%) in samples (Kopp 1969). Barium concentrations in surface water and drinking water range from ≤5 to 15,000 μg/L with mean concentrations generally ranging from 10 to 60 μg/L (Barnett et al. 1969; Bowen 1979; Durfor and Becker 1964; Durum and Haffty 1961; Elinder and Zenz 1994; EPA 2005; Kopp 1969; Kopp and Kroner 1967; Longerich et al. 1991; McCabe et al. 1970;

Neal et al. 1996; Saleh and Wilson 1999; Tuovinen et al. 1980). There are regional variances in the concentration of barium in surface waters within the United States where the lowest levels (mean value of 15 µg/L) are found in the drainage basins of the western Great Lakes and the highest levels (mean values of 90 µg/L) are found in the drainage basins of the lower Mississippi Valley (EPA 2005). In the United States, barium concentrations in drinking water are generally below 200 µg/L with a mean concentration of 28.6 µg/L (EPA 2005). In California, drinking water contains barium at concentrations which are higher than the U.S. average, ranging between 101 and 280,280 µg/L with mean and median values of 302 and 160 µg/L, respectively (Storm 1994). Drinking water supplies obtained from groundwater contain barium at concentrations that are known to exceed the maximum contaminant level (MCL) of 2,000 µg/L (EPA 2002). In northeastern Illinois, Kentucky, Pennsylvania, and New Mexico, barium concentrations in drinking water obtained from groundwater are up to 10 times higher than the MCL (EPA 2005). These high levels of barium may be due to the leaching or erosion of barium from sedimentary rocks (Calabrese 1977; Kojola et al. 1978). However, in Texas, barium concentrations in groundwater are also high (1.2–2,300 µg/L) near brine injection, dry, or plugged gas/oil wells (Hudak and Wachal 2001). Barium has been detected in surface water and groundwater samples collected at 257 and 561 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. In surface water (lakes, streams, ponds, etc.), barium concentrations range from 0.33 to 18,100,000 ppb in 77 onsite samples (HazDat 2006). In comparison, concentrations of barium in surface water range from 10 to 73,800 ppb in 112 offsite samples (HazDat 2006). The concentrations of barium in groundwater range from 0.064 to 2,100,000 ppb in 442 onsite samples (HazDat 2006). In comparison, concentrations of barium in groundwater range from 0.05 to 803,000 ppb in 260 offsite samples (HazDat 2006). Concentrations of barium in leachate from municipal landfills ranged from 0.11 to 9,200 µg/L (EPA 1990; Roy 1994).

Barium has frequently been detected in soils in the 15–5,000 ppm range (Bowen 1979; EPA 1995a; Kabata-Pendias and Pendias 1984; Lide 2000; Schroeder 1970; Shacklette and Boerngen 1984; Zenz et al. 1994). Regional differences exist for barium concentrations in subsoils where mean concentrations and ranges in the eastern United States of 300 and 15–1,000 ppm, respectively are lower than the values of 560 and 70–5,000 ppm, respectively, for barium concentrations in the western United States (Bowen 1979; Schroeder 1970; Shacklette and Boerngen 1984). Bradley et al. (1994) reported that barium concentrations measured in topsoil

(0–6 inch depth) samples taken from three New England cities were not influenced by industrial activity. Barium concentrations in sediments have been found to exceed EPA guideline concentrations of 20–60 µg barium/g dry weight at 13 of 16 sites sampled along the southeastern shore of Lake Erie and the southern shore of Lake Ontario (Lowe and Day 2002) and in sediments taken from Lake Pontchartrain near New Orleans where a mean value of 482.1 µg/g was obtained (USGS 2005). Barium has been detected in soil and sediment samples collected at 369 and 260 of the 798 hazardous waste sites, respectively, where barium has been detected in some environmental medium (HazDat 2006). The HazDat information includes data from both NPL and other Superfund sites. Concentrations of barium in soil (topsoil, <3 inches depth) ranged from 1.59 to 13,000 ppm in 84 onsite samples (HazDat 2006). In comparison, concentrations of barium in soil (topsoil, <3 inches depth) ranged from 3 to 54,700 ppm in 28 offsite samples (HazDat 2006). Concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 13.1 to 17,600 ppm in 36 onsite samples (HazDat 2006). In comparison, concentrations of barium in sediment (lakes, streams, ponds, etc.) ranged from 0.156 to 26,400 ppm in 92 offsite samples (HazDat 2006).

In cultivated plants such as cabbage, corn, lima beans, soybeans, and tomatoes, the concentration of barium ranges between 7 and 1,500 ppm (Connor and Shacklette 1975). It was found in a Canadian Total Diet Study that barium concentrations in a wide variety of foods are generally low, measuring <4 ppm (Health Canada 2005). However, Brazil nuts have a high concentration of barium ranging between 3,000 and 4,000 ppm (Beliles 1979).

***Priority Recommendation*:** The identified data need is not considered priority. Reliable and current monitoring data for the levels of barium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of barium in the environment and the resulting body burden of barium can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. However, ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 798 NPL sites at which barium has been found. This database includes maximum concentrations of barium in on- and off-site media, and an indication of relevant routes of exposure. Further evaluation of this database is needed before the need to collect additional media-specific data is assigned priority.

(2) Humans

***Purpose*:** To determine whether adequate data are available on the levels of barium in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need has been identified. No data are available on the levels of barium in body tissues or fluids for people living near hazardous waste sites.

Barium content in the general population in the United States has been determined in urine and major organs and tissues in more current studies. Barium concentrations in urine for the population aged 6 years and older were measured in the National Health and Nutrition Examination Survey (NHANES) of 2001-2002. The geometric mean (95% confidence interval) for the creatinine-adjusted levels of barium in urines for all ages was 1.44 (1.31–1.58) μg per gram of creatinine (CDC 2005). Within age groups, the geometric means for the barium concentration in urine decreased as a function of age, from 2.20 μg per gram of creatinine (6–11 years) to 1.45 μg per gram of creatinine (12–19 years) and 1.37 μg per gram of creatinine (20 years and older). The geometric mean concentration of barium in females (1.59 μg per gram of creatinine) was slightly higher than in males (1.30 μg per gram of creatinine). As a function of ethnicity, non-Hispanic whites had the highest geometric mean barium concentrations (1.62 μg per gram of creatinine) followed by Mexican-Americans (1.18 μg per gram of creatinine) and non-Hispanic African-Americans (0.891 μg per gram of creatinine).

***Priority Recommendation*:** The identified data need to collect additional information is not considered priority. Reference range concentrations of barium in urine are available for the adult populations (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites. Therefore, the identified data need is not considered priority at this time.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to barium are available for the purpose of conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to conduct additional studies to assess exposures of children to barium has been identified. There are no exposure studies of barium in children residing in the United States except for infants through the ingestion of breast milk, cow's milk, and baby formula (Biego et al. 1998). However, there are data on barium intake through the diet of children living in Canada that may be representative of children living in the United States. Daily barium dietary intakes determined from the Canadian Total Diet Study show that the highest barium intake (25.25 µg/kg body weight/day) is for children between the ages of 1 and 4 years (Health Canada 2005). For older children, the daily dietary intake of barium decreases to 18.74 µg/kg body weight/day for children 5–12 years and then to 11.76 and 9.28 µg/kg body weight/day for males and females ages 12–19 years, respectively. Data are also available for body burden measurements in children based on barium concentrations in urine. For children ages 6–11 years, the mean (geometric) barium concentration in urine was found to be 2.20 µg/g creatinine (CDC 2005). The barium concentrations in urine decreased with age to 1.45 and 1.37 µg/g creatinine for individuals with ages of 12–19 years and 20 years or older, respectively. However, there are no studies correlating exposure of children to barium and body burden measurements of barium. For children living near a hazardous waste site, the primary route of exposure for children to barium is through ingestion of drinking water or soil containing barium, or inhalation of dust containing barium. Also, children are likely to be exposed to barium from parent's clothing or other items removed from the work place. Although there have been no documented exposures of children to barium from pica, the intake of barium through ingestion of soil for these children could be considerable given that soil is the major reservoir of barium that is released to the environment.

***Priority Recommendation*:** The identified data need to conduct additional studies to assess exposures of children to barium is not considered priority. Reference range concentrations of barium in urine are available for children (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites. Therefore, the identified data need is not considered priority at this time.

e. Environmental Fate

***Purpose*:** To determine whether the available data are adequate to estimate exposure to barium under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need to determine the transport and transformation of barium in the atmosphere has been identified.

Barium is not expected to distribute widely when released to air. When released into air, barium is likely to be present in particulate form with removal from air largely occurring through dry and wet deposition (EPA 1984). The residence time for barium in air is expected to be much shorter than in water or soil, maybe several days, depending on the size of the particulate, the chemical nature of the particulate, and environmental factors such as rainfall (EPA 1984; WHO 2001).

In water, barium is not expected to distribute widely from where it is released with a limited lifetime for the soluble forms of barium. After release, soluble barium is expected to precipitate out of solution as insoluble salts (e.g., barium sulfate and barium carbonate) and settle into sediments. In fact, sedimentation of suspended solids removes a large portion of barium from surface waters (Benes et al. 1983). It is estimated that the sulfate concentrations in natural waters are at levels that limit the maximum solubility of barium in water to 1,000–1,500 µg/L (EPA 1983; Hem 1959; Lagas et al. 1984; McCabe et al. 1970). Lifetimes for the soluble forms of barium in natural waters could not be located. A number of factors determine the solubility of barium in water, including the pH and the concentrations of anionic species such as sulfate, carbonate, chloride, and nitrate. Sulfate levels appear to be the major factor for determining barium solubility given that barium found in sediments is largely in the form of barium sulfate (González-Muñoz et al. 2003). The precipitation of barium as barium sulfate is especially accelerated at the point where rivers empty into the ocean due to the high sulfate content (905 mg/L) of ocean water (Bowen 1966). At pH levels of 9.3 or below, the formation of barium sulfate limits the barium concentration in natural waters (Bodek et al. 1988). The presence of chloride (Cl^-) and other anions (e.g., nitrate [NO_3^-] and carbonate [CO_3^-]) increases the solubility of barium sulfate at pH 9.3 or below. In fact, the chloride, hydroxide, and nitrate salts of barium are frequently detected in aqueous environments (Bodek et al. 1988; EPA 1983; Kirkpatrick 1978). At pH >9.3 in the presence of carbonate, barium carbonate becomes the dominant species

in natural waters (Bodek et al. 1988; Singer 1974). Due to its very low solubility and fast precipitation kinetics, barium carbonate limits the soluble barium concentration under alkaline conditions (Faust and Aly 1981; Hem 1959; Rai et al. 1984; Singer 1974).

In soil, the mobility of barium is expected to be limited due to the formation of water-insoluble salts in soils and an inability to form soluble complexes with fulvic and humic acids (EPA 1984; WHO 2001). The movement of barium through soil is determined by the properties of the soil, including cation exchange capacity, calcium carbonate content, and pH (WHO 2001). Barium mobility is limited in soils with high cation exchange capacity (e.g., fine textured mineral soils and soils containing a high amount of organic matter) and high calcium carbonate content (Bates 1988; Kabata-Pendias and Pendias 1984; Lagas et al. 1984). Barium binds to soil either through reactions with metal oxides (e.g., Al_2O_3, MnO_2, SiO_2, and TiO_2) and hydroxides or through electrostatic interactions (Bodek et al. 1988; Hem 1959; Rai et al. 1984; Singer 1974). Barium is strongly absorbed by clay minerals (Bodek et al. 1988). It has been suggested that these interactions with soil components probably act to control the concentrations of barium in natural waters (Bodek et al. 1988). Barium is more mobile in soils with high chloride content or lower pHs as water-insoluble barium salts such as barium sulfate and barium carbonate become more soluble (Bates 1988; Lagas et al. 1984; WHO 2001). In soils affected by acidic landfill leachate, barium will be much more mobile due to the formation of complexes with fatty acids and other organics present in leachate (Lagas et al. 1984).

***Priority Recommendation*:** The identified data need is not considered priority. Although it is important to understand the transport and transformation of barium in the atmosphere, it is recognized that the primary release medium of barium in the environment is to water and soil. In surface water and soil, the fate of barium is well understood. Although the environmental fate of barium in air is understood to be largely determined by wet and dry deposition processes, there is limited information on range of transport and the chemical transformations that barium may undergo in the particulate matter to which it is bound in air.

f. Bioavailability and Bioaccumulation Potential

***Purpose*:** To determine whether adequate data are available to predict the potential of barium to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

***Finding*:** A data need to determine the bioavailability in soil has been identified. Based on TRI data, the largest release of barium is to soils (TRI04 2006). Also, soils are expected to be a reservoir for barium due to the very limited mobility of barium in soils. Ingestion of soil may be a significant source of barium intake, especially for individuals living near hazardous waste sites and children with pica behavior. The bioavailability of barium in soil will depend on the chemical form of barium. Soils containing barium carbonate are expected to provide a more bioavailable form of barium than soils containing barium sulfate due to the solubility of barium carbonate in acidic solutions (Budavari et al. 2001), such as those encountered in stomach fluids. However, bioavailability of barium from soil has not been studied.

A second data need to examine the bioconcentration of barium in plants and terrestrial animals and the biomagnification of barium in aquatic and terrestrial food chains has also been identified. Barium is found to bioconcentrate in marine plants and marine and freshwater animals. Bioconcentrations factors ranging between 400 and 4,000 have been determined for a number of species of marine plants (Bowen 1966). In marine animals, bioconcentration factors averaging 100 have been reported (Schroeder 1970). For freshwater fish, a bioconcentration factor of 129 was provided by Hope et al. (1996). In terrestrial plants, the uptake and concentration of barium in plant tissues is small compared to the amount of barium in soils. For example, a bio-concentration factor of 0.4 has been estimated for plants in a Virginia floodplain with a barium soil concentration of 104.2 mg/kg (Hope et al. 1996). However, there are some plants, such as legumes, forage plants, brazil nuts, and mushrooms, that accumulate barium (Aruguete et al. 1998; IPCS 1991; WHO 2001). Bioconcentration factors from 2 to 20 have been reported for tomatoes and soybeans (WHO 2001). No studies of bioconcentration or biomagnification of barium in terrestrial animals could be located.

Priority Recommendation: The identified data need to determine the bioavailability of barium from soil is not considered a priority. Determining the bioavailability of barium from soil is important for assessing the amount of barium that is available through uptake from the gastrointestinal tract in comparison to amount ingested. However, for individuals living near hazardous waste sites, the number of those who may be exposed to barium through this exposure route is expected to be rather small compared to exposures through ingestion of drinking water contaminated with barium or inhalation of dust containing barium. The second data need, determining the bioconcentration of barium in plants and terrestrial animals and the

biomagnification of barium in aquatic and terrestrial food chains, is not considered a priority. The amounts of barium that are bioconcentrated in fish are rather low considering that barium concentrations in marine and fresh waters are also low. Based on a limited amount of data, the low bioconcentration factors of fish in comparison to aquatic plants suggest that biomagnification of barium in aquatic food chains does not appear to be occurring. For terrestrial plants, the bio-concentration factors tend to be very low except for some species of plants, including agricultural plants like soybeans and tomatoes. For those plants that provide a source of food for human populations, a better understanding of the factors that determine the extent that barium is bioconcentrated in plants is important for identifying methods for reducing exposure to barium through these food items. Given the low extent of bioconcentration of barium in terrestrial plants, biomagnification of barium in the terrestrial food chain is not expected to occur.

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to barium in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for selection as a primary contaminant to establish a barium subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. Barium has been found in at least 798 NPL hazardous waste sites. At this time, no formal registries exist that identify people known to have been exposed to barium. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to barium. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list barium as a contaminant and the size of the potentially exposed population.

***Priority Recommendation*:** The identified data need is not considered priority. The development of a barium subregistry at this time would not contribute significantly to the current database.

The development of an exposure subregistry should await the results of needed studies including information on exposure levels in populations living near hazardous waste sites.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- Studies available for all toxicological profile substances to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for barium. Please refer to the ATSDR Toxicological Profile for barium, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2007). Generally, ATSDR believes that the most relevant route(s) of human exposure to barium at waste sites is ingestion of barium in drinking water, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the oral route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a one-year exposure.

a. Acute-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Information on the toxicity of inhaled barium comes from a human experimental study in which welders were exposed to fumes from barium-containing electrodes (Zschiesche et al. 1992), a case of a worker exposed to a large amount barium carbonate dust (Shankle and Keane 1988), and a study in which guinea pigs were exposed to a single concentration of barium chloride for unspecific amount of time (Hicks et al. 1986). Although none of these studies are suitable for derivation of an MRL, the Hicks et al. (1986) study does identify two potential end points (increased blood pressure and bronchoconstriction). Additional inhalation studies are needed to characterize target organs and establish exposure-response relationships.

Most of the available information on the acute toxicity of barium comes from human case reports involving oral exposure to soluble barium compounds and oral toxicity studies in animals. There are a number of case reports of individuals accidentally or intentionally ingesting large 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; Talwar and Sharma 1979; Wetherill et al. 1981). In general, dose levels were not reported; based on the severity of the observed effects, it is likely that the doses were very high. The observed effects included effects associated with hypokalemia (cardiac arrest, ventricular tachycardia, muscle weakness, and paralysis), gastrointestinal distress (vomiting, gastric pain, and diarrhea), and kidney damage (hemoglobin in the urine, renal insufficiency, degeneration, and acute renal failure). The available oral exposure studies in animals have not consistently identified targets of toxicity or adverse effect levels (Borzelleca et al. 1988; NTP 1994). A well-designed drinking water study in rats and mice failed to identify adverse effects at doses as high as 110 mg/kg/day (NTP 1994). The available data were considered inadequate for derivation of an acute-duration oral MRL for barium. Although the available animal studies (Borzelleca et al. 1988; NTP 1994) have evaluated the toxicity of barium chloride in repeated dose studies; none of the studies have identified a non-lethal biologically significant adverse effect level. 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.

Human data consistently identify the gastrointestinal tract as a target of barium toxicity; most case reports of individuals ingesting soluble barium compounds report vomiting, diarrhea, and/or abdominal pain as one of the early signs of toxicity. However, none of the animal studies have adequately investigated this end point; rodents are not a good model for examining gastrointestinal irritation. Animal studies are needed to identify the critical targets of barium toxicity and establish dose-response relationships; these studies should include a more appropriate animal model for investigating potential gastrointestinal effects.

Information on the dermal toxicity of barium comes from a case report of an individual burned with molten barium chloride (Stewart and Hummel 1984) and a study examining the dermal and ocular toxicity of barium carbonate in several animal species (Tarasenko et al. 1977). The animal studies suggest that barium carbonate is a local irritant; however, poor reporting of the experimental design and results limits the interpretation of the study. Additional dermal toxicity

studies are needed to identify critical targets, particularly at remote sites, and to establish exposure-response relationships.

***Priority Recommendation*:** The identified data need to conduct additional studies via the oral route of exposure is considered priority. Additional 14-day oral studies in animals by the oral route are a priority to determine dose-response relationships for the effects of acute oral exposure to barium on a wide range of potential target tissues. These data are needed to provide a basis for the derivation of an acute oral MRL. The data needs for additional inhalation and dermal exposure studies are not considered priority because these are not the primary routes of exposure for individuals living near hazardous waste sites.

b. Intermediate-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional studies via inhalation, oral, dermal exposure has been identified. No human studies have examined the toxicity of barium in humans following intermediate-duration inhalation exposure. The two animal studies which examined the toxicity of inhaled barium (Cullen et al. 2000; Tarasenko et al. 1977) were considered inadequate for derivation of an intermediate MRL. Tarasenko et al. (1977) reported pulmonary lesions, increases in blood pressure, ECG alterations, decreased blood hemoglobin levels, decreased liver function, decreased body weight gain, altered spermatogenesis, testicular lesions, shortened estrus cycle, and developmental effects (reduced survival, underdevelopment, decreased weight gain, and hematological alterations). However, interpretation of this study is 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 Cullen et al. (2000) study only examined the respiratory tract. As these studies were considered inadequate for development of an inhalation MRL, additional inhalation studies examining a variety of end points are needed to identify the critical targets of barium toxicity and to establish exposure-response relationships.

Information on the oral toxicity of barium following intermediate-duration exposure comes from a human experimental study examining cardiovascular toxicity (Wones et al. 1990) and several animal studies examining systemic toxicity (McCauley et al. 1985; NTP 1994; Perry et al. 1983,

1985, 1989; Tardiff et al. 1980), neurotoxicity (NTP 1994), reproductive toxicity (Dietz et al. 1992; NTP 1994), and developmental toxicity (Dietz et al. 1992). The human study did not find significant alterations in blood pressure or ECG readings in adults exposed to fairly low doses (Wones et al. 1990). Effects observed in the animal studies include increased blood pressure (Perry et al. 1983, 1985, 1989), kidney damage (glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane and mild to moderate nephropathy) (McCauley et al. 1985; NTP 1994), and developmental toxicity (decreased pup birth weight) (Dietz et al. 1992). The increase in blood pressure was observed at the lowest adverse effect level; however, two other studies (McCauley et al. 1985; NTP 1994) did not find significant alterations in blood pressure or ECG readings in rats exposed to higher doses of barium. The low-mineral diet used in the Perry et al. (1983, 1985, 1989) studies may have 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 1995). Additional studies are needed to support this hypothesis. 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 following intermediate-duration oral exposure; an intermediate-duration oral MRL was derived based on kidney effects observed in rats exposed to barium chloride for 13 weeks (NTP 1994).

No studies have examined the toxicity in humans or animals following intermediate-duration dermal exposure. Studies are needed to assess the potential toxicity of various barium compounds and to establish whether dermal exposure would result in remote toxicity.

***Priority Recommendation*:** The need to conduct additional oral studies to explain the apparent differences between the Perry et al. (1983, 1985, 1989) study results and those by McCauley et al. (1989) and NTP (1994) are not considered priority because ATSDR considered the available oral toxicity database to be adequate for derivation of an MRL. Also, the need to conduct additional studies via inhalation or dermal exposure is not considered priority because these exposure routes are not considered the primary exposure routes at hazardous waste sites.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Three occupational exposure studies (Doig 1976; Essing et al. 1976; Seaton et al. 1986) have evaluated the chronic toxicity of inhaled barium. These studies focused on potential respiratory tract effects and are limited by co-exposure to other compounds, small number of tested workers, and/or lack of a comparison group. Well-designed studies examining a number of potential end points are needed to identify the critical targets of barium toxicity and establish exposure-response relationships.

Information on the chronic toxicity of ingested barium comes from two community-based studies that evaluated the possible association between elevated levels of barium in drinking water and increased risk of cardiovascular disease (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981) and several studies in rats and mice (NTP 1994; Perry et al. 1989; Schroeder and Mitchener 1975a, 1975b). One epidemiology study found no significant associations between living in a community with elevated barium levels and the prevalence of hypertension, heart disease, or stroke (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). The other study found a significantly higher mortality rate, particularly among individuals 65 years of age and older, for cardiovascular disease and heart disease (arteriosclerosis) in residents of a community with elevated barium drinking water levels (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981). A common limitation of these studies is the lack of information on tap water consumption, actual barium intakes, and duration of exposure and the lack of control for a number of potential confounding variables, particularly the use of water softeners. The Perry et al. (1989) rat study found significant increases in systolic blood pressure in rats; however, as discussed in the Intermediate-Duration Exposure section, the contribution of the low mineral basal diet to the observed effect is not known. Several rat studies did not find adverse effects at the highest doses tested (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a). Marked renal nephropathy was observed in mice (NTP 1994); this study and effect was the basis of the chronic-duration MRL for barium. The available toxicokinetic data suggest that barium

accumulates in bone; it is not known if this accumulation would result in adverse effects. However, in the NTP study (NTP 2004), no neoplastic or non-neoplastic lesions in bone or marrow (or changes in bone density in rats) associated with treatment were reported. Studies designed to test the possible association between high levels of barium in bone and adverse bone effects may be useful.

Data on the dermal toxicity of barium are limited to a skin tumor promotion study using barium hydroxide extract from tobacco plants (Van Duuren et al. 1968); the study did not examine noncancerous end points. Additional dermal exposure studies are needed to evaluate whether various barium compounds are irritants and can cause remote-site toxicity.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Oral exposure is the primary route of exposure for individuals living near hazardous waste sites; although there is a need to conduct additional studies to evaluate if long-term accumulation of barium in bones would result in adverse effects, the available chronic toxicity database was considered adequate for derivation of an oral MRL. The need for additional inhalation and dermal exposure studies was not considered priority because these exposure routes are not considered the primary exposure routes at hazardous waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to barium are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity end point assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

***Finding*:** A data need to conduct additional studies for the carcinogenicity of barium via inhalation and dermal exposure has been identified. No studies assessing the carcinogenicity of barium following chronic inhalation exposure were identified. The carcinogenicity of ingested barium has been assessed in several long-term oral exposure studies in rats and mice (McCauley et al. 1985; NTP 1994; Schroeder and Mitchener 1975a, 1975b). These studies did not find significant alterations in the incidence of neoplastic lesions in either species. Although the Van Duuren et al. (1968) study provided evidence suggesting that this barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent when applied with a tumor-initiating agent, there are no studies to assess barium's potential to be a complete carcinogen following dermal exposure. Based on the results of the oral studies, it can be predicted that inhalation or dermal exposure to barium would not likely result in remote site carcinogenicity; however, it is not known if long-term exposure would result in respiratory tract cancer following inhalation exposure or skin cancer following dermal exposure. Inhalation and dermal exposure cancer studies are needed to address these questions. The Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not classified barium as to its carcinogenicity. The EPA has concluded that barium is not classifiable as to human carcinogenicity, Group D (IRIS 2005). However, under EPA's revised guidelines for carcinogenic 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 (IRIS 2005).

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because these routes are not considered to be the primary exposure routes at hazardous waste sites.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of barium-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Finding*:** A data need to conduct additional genotoxicity studies has been identified. The genotoxicity of barium has not been well characterized. One study used an *in vivo* assay to assess genotoxic potential (Yesilada 2001); increases in somatic mutations were observed in *Drosophila melanogaster* following exposure to high levels of barium nitrate. The available data utilizing *in vitro* assays have not found significant alterations in gene mutation frequency or DNA damage in non-mammalian systems (Kanematsu et al. 1980; Monaco et al. 1990, 1991; Nishioka 1975; NTP 1994; Rossman et al. 1991; Sirover and Loeb 1976a, 1976b). In mammalian test systems, barium did not have clastogenic effects (NTP 1994), but did increase the frequency of gene mutation (NTP 1994). The available data are inadequate to thoroughly assess the genotoxic potential of barium; additional studies, particularly *in vivo* assays, are needed.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity tests is not considered priority. Although additional in vivo genotoxicity studies would be helpful to evaluate the potential genotoxicity of barium, these studies are not given priority because barium has not been shown to be carcinogenic by the oral route.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to barium are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level

studies include, but are not limited to, *in vitro* studies (e.g., [1] Estrogen Receptor Binding/Transcriptional Activation Assay, [2] Androgen Receptor Binding/Transcriptional Activation Assay, and [3] Steroidogenesis Assay with Minced Testis), and *in vivo* studies (e.g., [1] Rodent 3-day Uterotropic Assay, [2] Rodent 20-day Pubertal Female Assay with Thyroid, [3] Rodent 5–7 day Herschberger Assay).

If any of the following is true, then ATSDR will consider assigning Level II priority to 2-generation reproductive studies: if (1) there are suggestions that barium may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following barium exposure; or (3) if there are structurally similar compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Findings*:** A data need to conduct additional studies on the endocrine system via inhalation, oral, and dermal exposure has been identified. There are no human or animal data on the potential of barium to disrupt the endocrine system. The available experimental animal systemic (NTP 1994), developmental (Dietz et al. 1992), and reproductive toxicity (Dietz et al. 1992) studies did not indicate any effects that are suggestive of endocrine disruption. Additional *in vitro* and *in vivo* studies designed to assess endocrine disruption would be useful.

***Priority Recommendation*:** The identified data need to conduct additional studies on the endocrine system via inhalation, oral, and dermal exposure is not considered priority. There are no data to suggest that the endocrine system would be a target of toxicity for barium. The recommended *in vitro* and *in vivo* endocrine disruption screening studies should provide sufficient information to evaluate the sensitivity of this end point.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to barium are at an increased risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data

in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need to conduct additional reproductive studies via inhalation, oral, or dermal exposure has been identified. The reproductive effects of barium have not been thoroughly studied. There are no studies regarding reproductive effects in humans following barium exposure. Several animal studies have examined potential end points of reproductive toxicity. In the only inhalation exposure study (Tarasenko et al. 1977), a number of adverse effects were reported, including disturbances in spermatogenesis, shortened estrus cycle, and histological damage to the testes and ovaries. However, the poor reporting of the study design and results (including incidence data and statistical analysis) limits the interpretation of the study results. Although a 10-day gavage study reported significant decreases in relative and absolute ovary weights (Borzelleca et al. 1988), other oral exposure studies have not found alterations in organ weights or histological alterations in reproductive tissues following acute-, intermediate- or chronic-duration exposure (McCauley et al. 1985; NTP 1994). Additionally, no alterations in sperm morphology, motility, or counts were observed in rats or mice exposed to barium in drinking water for 60 days (Dietz et al. 1992). A two-generation study would be useful for further evaluating the potential reproductive toxicity of barium. Only one oral study evaluated reproductive function (Dietz et al. 1992) and reported no alterations in pregnancy rate or gestation length in rats or mice. No dermal exposure studies examining reproductive end points were

identified. Additional studies are needed to further assess if reproductive toxicity is an end point of concern for barium.

***Priority Recommendation*:** The identified data need to conduct additional reproductive toxicity studies via inhalation, oral, or dermal exposure is not considered priority. For the primary route of exposure, the oral route, the available data do not provide suggestive evidence that the reproductive system is a sensitive target of toxicity; thus, the need for additional oral reproductive toxicity studies is not considered priority. The need for inhalation and dermal exposure studies is not considered priority because these are not the primary routes of exposure for populations living near hazardous waste sites.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to barium are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that, in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of barium, (2) if there are human anecdotal reports of developmental effects following barium exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

***Finding*:** A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. The developmental effects of barium have not been studied extensively in either humans or animals. One limited statistical study evaluated the degree of correlation between barium concentrations in drinking water and human congenital malformation

rates of the central nervous system (Morton et al. 1976). Results of the study indicated that there was a negative statistical correlation between these parameters, implying that a lower risk of congenital abnormalities was found in populations with higher barium levels. Two animal studies evaluated the potential developmental toxicity of barium. Reduced survival, underdevelopment, lowered body weight, decreased lability of the peripheral nervous system, and various blood disorders were reportedly noted in the offspring of rats following inhalation to barium for an intermediate exposure period (Tarasenko et al. 1977). The investigators also noted increased mortality and systemic toxicity in the offspring of rats orally exposed to barium during conception and pregnancy. As noted previously, interpretation of the results from the Tarasenko et al. (1977) studies are limited because the studies were poorly reported and no incidence data or statistical analysis were reported. In a developmental toxicity study involving oral exposure to barium chloride prior to mating (Dietz et al. 1992), decreases in pup body weight and a nonstatistically significant decrease in live litter size were observed in rats; the LOAEL for developmental effects was also associated with decreases in maternal body weight gain and water consumption. No adverse effects were observed in mice. Additional developmental toxicity studies, particularly studies involving oral exposure during gestation and lactation, are needed to confirm the results of the Tarasenko et al. (1977) and Dietz et al. (1992) studies; these studies should be conducted via the inhalation and oral routes. Developmental toxicity studies via dermal exposure are also needed because this end point has not been evaluated for this route of exposure.

***Priority Recommendation*:** The identified data need to conduct additional developmental toxicity studies via oral exposure is not considered priority. Although the results of the Dietz et al. (1992) mating study provide suggestive evidence that the developing organism may be a target, it is not known if the decrease in pup body weight was secondary to decreases in maternal body weight gain and water consumption or was a direct effect on the fetus. In addition, there are no human anecdotal reports of developmental effects following barium exposure. Therefore, additional studies via oral exposures to further evaluate this potential effect are not considered priority. Also, the need for inhalation and dermal exposure studies is not considered a priority because these are not the primary exposure routes for populations living near hazardous waste sites.

h. Immunotoxicity

***Purpose*:** To evaluate the mechanism of barium-induced toxicity for purposes of defining target organs and future mitigation activities. There is evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the evaluation of the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. The effect of barium on the immune system has not been well studied. No studies were available regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to barium. Several oral exposure studies in animals examining lymphoreticular end points such as thymus and lymph node histopathology have not reported adverse effects at nonlethal doses (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994). Screening studies are needed to evaluate the potential immunotoxicity of barium following inhalation, oral, or dermal exposure.

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via inhalation, oral, or dermal exposure is not considered priority because the available evidence from intermediate- and chronic-duration studies via oral exposure does not suggest that barium adversely affects the immune system. In addition, inhalation and dermal exposures are not the primary exposure routes for populations living near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of barium-induced toxicity to define target organs and future mitigation activities. Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the

absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure has been identified. Absence of a deep tendon reflex has been reported in an individual exposed to airborne barium carbonate powder (Shankle and Keane 1988). Exposure to high oral doses of barium is associated with numbness and tingling around the mouth and neck (Lewi and Bar-Khayim 1964; Morton 1945); higher doses can result in partial or complete paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Oral exposure of rats and mice to barium has not been associated with changes in brain weight or gross or microscopic lesions of the brain (Borzelleca et al. 1988; McCauley et al. 1985; NTP 1994; Tardiff et al. 1980). NTP (1994) evaluated neurobehavioral performance in rats and mice exposed to barium chloride in drinking water for acute or intermediate durations. Decreases in spontaneous motor activity were observed in rats exposed for an intermediate duration. Decreased grip strength was also observed in mice; however, this was likely due to debilitation rather than neurotoxicity. The human data demonstrate that at presumably high doses, barium affects action potentials of muscles and nerve cells by increasing cellular potassium levels. However, oral studies are needed to establish a dose-response relationship for these neurological effects. No data were available regarding neurological effects in animals following inhalation exposure or humans and/or animals following dermal exposure. Additional studies would be useful to further evaluate the neurotoxic potential of barium.

***Priority Recommendation*:** The identified data need to conduct additional neurotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. The nervous system is a target following high-dose exposure to barium, but does not appear to be a sensitive target following low-dose exposure. Thus, priority is not assigned to the oral exposure studies. Priority

is not assigned to the inhalation and dermal exposure studies because these are not the primary routes of exposure at hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of barium across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

***Finding*:** A data need to assess the toxicokinetics of barium following inhalation, oral, and dermal exposure has been identified. The database on absorption, distribution, metabolism, and excretion of barium is limited. Existing studies indicate that barium is absorbed from the respiratory tract (Cuddihy and Griffith 1972; Cuddihy and Ozog 1973; Morrow et al. 1968) and gastrointestinal tract (Cuddihy and Griffith 1972; Harrison et al. 1956; Leggett 1992; LeRoy et al. 1966; Schroeder et al. 1972; Taylor et al. 1962; Tipton et al. 1969), primarily deposited in the bones and teeth (Bauer et al. 1957; Cuddihy and Griffith 1972; Losee et al. 1974; Miller et al. 1985; Moloukhia and Ahmed 1979; Sowden 1958; Sowden and Pirie 1958; Sowden and Stitch 1957), and excreted mostly in feces and urine (Cuddihy and Griffith 1972; Tipton et al. 1966). Deposition in bones and teeth and excretion in feces and urine appear to be independent of the route of exposure. Essentially no data exist on absorption, distribution, or excretion following dermal exposure; however, this route is not considered to be a significant source of exposure to barium. No significant data exist on the metabolism of barium compounds in the body. Additional studies evaluating the binding and/or complexing of barium and barium compounds with biological macromolecules or organic molecules in the body would be useful. Studies quantifying the extent of absorption following inhalation, oral, and dermal exposure also would be useful because of limited absorption data. A wide variety of individual differences in absorption efficiencies have been detected in the available human studies; studies examining factors influencing barium absorption would be useful.

The available data in laboratory animals suggest that the toxicity of ingested barium is similar across species. Studies conducted by NTP (1994) in rats and mice found similar targets of toxicity. Although some apparent differences in sensitivity were found across the species, they were equally sensitive when the dose was estimated on a per unit surface area rather than a per unit body weight. In the absence of contrary data, it is assumed that humans and animals would

have similar targets of toxicity and sensitivity. Based on the available data, there do not appear to be significant differences in the toxicokinetics of barium between species (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and Washington 1983), although there is some indication that a larger percentage of absorbed barium is excreted in the feces of humans compared to that of experimental animals. However, there are not enough similar studies on different species to determine this with certainty. Studies on different species would increase confidence in the reliability of the existing database.

***Priority Recommendation*:** The identified data need to assess the toxicokinetics of barium following inhalation, oral, and dermal exposure is not considered priority. Although additional studies would be useful, the available oral studies provide adequate information to determine that barium is partially absorbed, primarily distributed to the bone, and excreted in the feces and urine. Data are insufficient for comparing across exposure routes. Comparative studies are not considered priority because inhalation and dermal contact are not considered the primary exposure routes for individuals living at hazardous waste sites.

2. Level III Data Needs

a. Epidemiologic Studies

***Purpose*:** To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

***Finding*:** A data need has been identified. A limited number of epidemiological and human dosimetry studies evaluating the health effects of barium are available (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974; Wones et al. 1990). These studies have primarily focused on the potential of barium to adversely affect cardiovascular function by altering blood pressure or increasing the risk of death due to cardiovascular disease; consistent results have not been found. However, all of the available human studies on barium have limitations and/or confounding variables that make it difficult to draw firm conclusions regarding the health effects of barium. Several human studies have also examined the potential toxicity of inhaled barium to the respiratory tract or cardiovascular system (Doig 1976; Essing et al. 1976; Seaton et al. 1986). As with the oral studies, limitations in the

study reporting or confounding variables preclude using the studies to establish causal relationships. In addition to these epidemiological or experimental studies, there are numerous case reports of individuals ingesting large doses of barium (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981) or exposed to airborne barium carbonate (Shankle and Keane 1988). In general, these studies reported serious health effects such as death, ventricular tachycardia, and paralysis. Animal studies provide evidence that the kidney is a sensitive target of toxicity; there is also some evidence that the cardiovascular and neurological systems and the developing organisms might be targets of barium toxicity (Dietz et al. 1992; McCauley et al. 1985; NTP 1994; Perry et al. 1983, 1985, 1989). Additional epidemiological and/or human dosimetry studies would be useful to determine the effects of low doses of barium on these end points. Studies of workers exposed to airborne barium would also be useful for establishing the toxicity of barium to the respiratory tract.

Priority Recommendation: The identified data need to conduct epidemiologic studies on barium is not considered priority. Barium has been detected in at least 798 of the 1,684 current or former NPL hazardous waste sites in the United States (HazDat 2006). Studies of populations living near sites contaminated with barium are likely to be confounded by exposure to other chemicals. If either worker or general populations with appropriate exposures can be identified, epidemiologic studies should be undertaken.

b. Mechanism of Toxic Action

***Purpose*:** To evaluate the mechanism of barium-induced toxicity to define target organs and future mitigation activities.

***Finding*:** A data need has been identified. No studies were located for animals or humans that describe observed mechanisms for barium absorption across the skin, lung, or gut; barium distribution; or barium excretion. The mechanism of barium toxicity has not been fully elucidated. High-dose exposure to barium consistently results in a number of effects including ventricular tachycardia, hypertension and/or hypotension, and muscle weakness and paralysis (Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Jha et al. 1993; Koch et al. 2003; Talwar and Sharma 1979; Wetherill et al. 1981). There is strong evidence that

many of these effects result from increases in intracellular potassium levels; hypokalemia (serum potassium levels below 3.5 mEq/L) has been reported in a number of individuals exposed to high doses of barium. The increased intracellular potassium levels results in a decreased resting membrane potential, making the muscle fibers electrically unexcitable and causing paralysis (Koch et al. 2003). Intravenous infusion of potassium often relieves many of the symptoms of barium toxicity (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). However, there is also evidence that some of these effects may be due to barium-induced neuromuscular blockade and membrane depolarization (Phelan et al. 1984; Thomas et al. 1998). Two investigators (Phelan et al. 1984; Thomas et al. 1998) have shown an apparent direct relationship between serum barium levels and the degree of paralysis or muscle weakness in two individuals orally exposed to barium. Additional studies are needed to fully elucidate this mechanism.

Animal studies provide evidence that the kidney is the most sensitive target of barium toxicity following longer-term oral exposure to lower levels of barium (NTP 1994). Studies are needed to examine the mechanisms resulting in kidney damage. Knowledge of such mechanisms would be useful in predicting species, route, and duration differences in toxicity.

***Priority Recommendation*:** The identified data need is not considered priority. Although research is needed for further elucidation of mechanisms of barium toxicity, this research is not given high priority at this time because of the need to further define targets of low-level exposure in humans and to identify threshold levels that cause adverse health effects.

c. Biomarkers

***Purpose*:** To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

***Finding*:** A data need has been identified. There are no established biomarkers of exposure for barium. Analytical methods exist for measuring barium in blood, urine, feces, and biological tissues (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987); however, there are no data correlating levels of barium in these tissues and fluids with exposure. Studies associating barium levels in biological media (such as blood or urine) with exposure concentrations or doses would be useful for establishing biomarkers of exposure. Symptoms of barium toxicity, such as hypokalemia, gastrointestinal upset, hyper- or hypo-tension, ventricular tachycardia, and

numbness and tingling around the mouth and neck (Das and Singh 1970; Deng et al. 1991; Diengott et al. 1964; Downs et al. 1995; Gould et al. 1973; Koch et al. 2003; Lewi and Bar-Khayim 1964; McNally 1925; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981), are well documented. However, there are no quantitative studies correlating these effects with dose and these effects are not specific to barium toxicity. For purposes of facilitating medical surveillance, studies to determine useful biomarkers of effect for barium, particularly effects associated with low doses of barium, would be useful.

***Priority Recommendation*:** The identified data need is not considered priority. Although there is no specific biomarker of effect for barium, a specific biomarker is not considered essential to conduct human studies because there is no unique disease associated with barium exposure.

d. Clinical Methods for Mitigating Toxicity

***Purpose*:** To determine whether any efforts are currently under way to mitigate the effects of exposure to barium.

***Finding*:** A data need has been identified. Methods have been reported for limiting oral and dermal absorption of barium compounds (Bronstein and Currance 1988; Dreisbach and Robertson 1987; Haddad and Winchester 1990) and for counteracting the hypokalemia that is produced by barium in acute high-level exposure situations (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). Contradictions exist in the literature regarding the efficacy or desirability of administering emetics (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional studies clarifying this issue would be helpful. Also, studies directed at finding a more efficient way to remove barium from the body would be useful. It is unclear whether mechanisms other than hypokalemia contribute to the toxic effects produced in acute high-level exposure situations. Additional information on the mechanisms responsible for the toxic effects of barium could aid in the development of effective treatments. Magnesium has been reported to antagonize the neuromuscular effects (Dreisbach and Robertson 1987). Additional studies examining the efficacy of administering soluble magnesium salts to antagonize the effects of barium would also be helpful. No information was located on treatment strategies for long-term, low-level exposures. Research on procedures for mitigating such chronic exposure situations would be helpful.

***Priority Recommendation*:** The identified data need is not considered priority. The mechanism of action has not been fully elucidated, no unique disease has been associated with barium exposure, and populations with specific substance-induced adverse health effects have not been identified.

e. Children's Susceptibility

***Purpose*:** To determine whether adequate data exist to identify potential health effects from exposures to barium during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

***Finding*:** A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above. There is very little information on the toxicity of barium in children. Two reports of food poisonings with barium carbonate (Deng et al. 1991; Lewi and Bar-Khayim 1964) provide some suggestive information that children may not be as sensitive as adults to barium carbonate toxicity; however, the lack of detailed examination of the exposed children and lack of exposure information limits the interpretation of these data. No human or animal toxicity studies have been designed to assess possible age-related differences in the toxicity of barium. There is some information suggesting that infants and young children may have a higher barium absorption rate than adults (ICRP 1993; Taylor et al. 1962). Other potential toxicokinetic differences have not been thoroughly investigated. Additional studies are needed to evaluate potential age-specific differences in toxicity and toxicokinetics.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via inhalation, oral, and dermal exposure is not considered priority. Additional studies on mechanisms of action and toxicokinetics of barium in immature and adult animals need to be conducted and evaluated before assigning priority to the identified data need.

IV. Summary: Prioritization of Data Needs for Barium

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for barium and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on barium, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on barium. Although a lot of information is available, a need to evaluate existing data on concentrations of barium in contaminated environmental media at hazardous waste sites has been identified.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 798 NPL sites at which barium has been found. This database includes maximum concentrations of barium in on- and off-site media, and an indication of relevant routes of exposure. Further evaluation of this database is needed before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of barium (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers. Although there is a need to collect data on levels of barium in body tissues and fluids for populations living near hazardous waste sites, it is not considered a priority at this time because reference range concentrations of barium in urine are available for children and the adult populations (CDC 2005). ATSDR acknowledges that reference concentration data can support exposure and health assessments at waste sites, but the Agency also continues to recognize the importance of collecting additional data on uniquely exposed populations at waste sites.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- None of the identified exposure data needs are considered to be priority at this time.

B. Toxicity

The toxicity of barium has been studied in animals by the oral exposure route. For this route of exposure, the kidney appears to be the primary target of toxicity. Human data suggest that electrolyte balance, cardiovascular system, neuromuscular system, and gastrointestinal tract are targets following exposure to high doses of barium. Additional acute oral exposure studies are needed for identifying sensitive targets, establishing dose-response relationships, and deriving an acute-duration oral MRL.

This nonhuman research need is justified because of the widespread domestic and environmental contamination of barium, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data need (Table 3):

- Dose-response data for acute-duration via oral exposure

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Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/metabolites/ biomarkers	
	Structure-Activity relationships (SAR)		
Physical Chemical Properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure Levels	Production volume, Use, Release/ disposal — may be used in lieu of monitoring data	Monitoring in REM*	Human dosimetry studies
		Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
			Disease registries
		Exposures of children	
Environmental Fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies	
		Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-Day by relevant route 90-Day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended reproworkup in subchronic	2-Generation or continuous breeding	Biomarkers*
			Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for Barium

	EXPOSURE		
	Level I	Level II	Level III
Analytical			
Physical Chemical Properties	Partitioning between soil and water in different soil types		
Exposure Levels		Exp levels in env media	potential candidate for exposure registry
		Exp levels in humans	
		Exp levels in children	
Environmental Fate		Transport/transformation in air	
Bioavailability	soil	Bioconc/biomagnif in aquatic and terrestrial food chains	
	TOXICITY		
	Level I	Level II	Level III
Acute	inhal, *ORAL*, dermal		
Repeated	inhal, oral, dermal	Toxicokinetics	
Chronic		inhal, oral, dermal	epidem
Genotoxicity		Additional *in vivo* genotoxicity studies	mechanisms
Endocrine disruption	*In vitro* and *in vivo* screen		
Reproductive toxicity		inhal, oral, dermal	Biomarkers
			Clinical methods for mitigating toxicity
Developmental toxicity		inhal, oral, dermal	
Children's susceptibility			inhal, oral, dermal
Immunotoxicity	inhal, oral, dermal		
Neurotoxicity	inhal, oral, dermal		
Carcinogenicity		Inhal, dermal	

UPPER CASE: Priority data needs identified for barium.