

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 silica is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of silica.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to silica that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of silica. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 Identification of Data Needs

A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

For c-silica, the focus of data needs is on the primary health effects associated with inhalation exposure in occupational settings (silicosis, lung cancer, COPD, kidney effects, tuberculosis, and autoimmune disorders). In addition, numerous studies show that c-silica is genotoxic. The extensive epidemiological literature does not identify any other adverse health effects. Thus, data needs for c-silica compounds is limited to discussions of these known effects. Given the extensive data gaps for inhaled a-silica,

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comprehensive evaluations of data needs were considered. Oral and dermal exposures are not considered as major routes of exposure for silica compounds; therefore, data needs for these routes were not evaluated.

MRLs. Note that available information on oral exposure of humans or animals to c-silica and a-silica does not identify critical targets for toxicity. Therefore, oral exposure to c-silica and a-silica does not appear to be an exposure route of concern. It is not anticipated that additional studies would provide information to derive oral MRLs for any duration for c-silica or a-silica.

Acute-Duration Inhalation MRL

Crystalline Silica. Adverse effects of occupational (inhalation) exposure to c-silica are not associated with exposure durations of ≤ 14 days. Additional studies are unlikely to identify effects of acute inhalation exposure to c-silica.

Amorphous Silica. The database is lacking studies evaluating the effects of acute-duration inhalation exposure to a-silica in humans. The database is also lacking studies evaluating the effects of acute-duration inhalation exposure to natural a-silica in animals. However, data are adequate to identify the critical effect following acute exposure to synthetic a-silica in animals. Available data indicate that the primary target of acute toxicity is the respiratory system; however, the potency differed between polymorphs. The lowest identified NOAEL and LOAEL values were 1 and 5 mg/m³, respectively, which were associated with transient pulmonary lesions after exposure to precipitated or pyrogenic a-silica for 5 days; similar effects were not observed with a-silica gel until 25 mg/m³ (Arts et al. 2007). In another study, markers of pulmonary inflammation following exposure to colloidal silica for 2 weeks were observed at ≥ 50.5 mg/m³, but not 10 mg/m³; exposure to precipitated a-silica induced these effects after a 3-day exposure to 10 mg/m³ (Warheit et al. 1991, 1995). Based on these findings, precipitated and pyrogenic silica may be more potent pulmonary toxicants than a-silica gel or colloidal silica; however, data are insufficient to evaluate potential differences in potency between precipitated and pyrogenic silica. Additional acute inhalation studies evaluating dose- and duration-dependence of respiratory effects for multiple polymorphs may establish clear potency relationships, allowing for derivation of an MRL based on the most sensitive polymorph(s).

Intermediate-Duration Inhalation MRL

Crystalline Silica, Inhalation. Intermediate-duration inhalation exposure typically is not associated with adverse health effects in workers, although occupational exposure to high levels (not defined; also called ‘intense exposure’) of respirable c-silica, such as in sand blasting, may cause accelerated silicosis (Beckett 1997; Leung et al. 2012). Accelerated silicosis may occur after weeks of intense exposure, but typically occurs 5–10 years after the start of exposure. Results of available occupational studies do not provide information on dose- or duration-dependence of intermediate-duration exposure associated with the development of accelerated silicosis. Therefore, additional occupational exposure studies of workers with accelerated silicosis that provide exposure-response and duration-response data may define the NOAEL and LOAEL values for accelerated silicosis associated with intense exposure.

Amorphous Silica, Inhalation. The database is lacking studies evaluating the effects of intermediate-duration inhalation exposure to a-silica in humans. However, data are adequate to identify the critical effect following intermediate exposure to synthetic a-silica in animals. Available data indicate that the primary target of intermediate toxicity is the respiratory system following exposure to different synthetic a-silica polymorphs. However, only limited data are available regarding the relative potency of polymorphs following intermediate-duration exposure. The lowest LOAEL identified was 1 mg/m³ for 13-week exposure to pyrogenic a-silica, which was associated with increased cellularity, inflammation, and fibrosis; a NOAEL was not identified (Reuzel et al. 1991). Similar effects were observed at the lowest tested concentration of 30 mg/m³ for precipitated a-silica (Reuzel et al. 1991). For colloidal silica, NOAEL and LOAEL values of 10 and 50 mg/m³, respectively, were identified for pulmonary inflammation and hyperplasia (Lee and Kelly 1992). No intermediate-duration inhalation studies were identified for a-silica gel. Respiratory effects were also the critical effect in the only available animal study evaluating natural a-silica; macrophage infiltration and alveolar epithelization were observed following exposure to raw diatomaceous earth at a TWA dose of 72 mg/m³ (only concentration tested) (Tebbens et al. 1957). Other systemic effects reported in intermediate-duration inhalation studies in animals included hematological effects following exposure to pyrogenic a-silica at 30 mg/m³ (Schepers et al. 197). Given the lack of a NOAEL value for diatomaceous earth and precipitated and pyrogenic a-silica, well-designed intermediate-duration inhalation toxicity studies with natural a-silica and multiple polymorphs of a-silica could provide more information regarding comparative potencies across a-silica forms and establish NOAEL values for respiratory effects.

Chronic-Duration Inhalation MRL

Crystalline Silica, Inhalation. The available database for chronic-duration occupational exposure to c-silica is extensive and identifies silicosis, lung cancer, COPD, renal effects, tuberculosis, and autoimmune disorders as targets. Of these, silicosis is considered to be the most sensitive effect. For all health effects, comparison of exposure-response data across studies can be challenging due to potential differences in toxicological potency of c-silica polymorphs and exposures to co-contaminants. Additional occupational exposure studies providing quantitative information of c-silica polymorphs and co-contaminants may provide useful information to determine the basis of differences in study results from different occupational cohorts.

Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis (Checkoway et al. 1997; Chen et al. 2001, 2012; Churchyard et al. 2004; Hedlund et al. 2008; Hnizdo and Sluis-Cremer 1993; Hughes et al. 1998, 2001; Kreiss and Zhen 1996; Mannelje et al. 2002a, 2002b; McDonald et al. 2005; Muir et al. 1989a, 1989b; Mundt et al. 2011; Steenland and Brown 1995a; Vacek et al. 2011). However, the low end of the exposure-response curve is not well-defined, with silicosis and death due to silicosis observed for the lowest cumulative exposure ranges reported. For the lowest estimated cumulative exposure range of 0–0.2 mg/m³-year, silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). For mortality due to silicosis, the lowest estimated cumulative exposure range of 0.1–1.23 mg/m³-year was associated with an increased risk of mortality (hazard ratio: 1.89; 95% CI: 1.60, 2.24) (Chen et al. 2012). Additional occupational studies focused on lower c-silica exposures may provide information to identify no-effect levels or threshold levels for silicosis or mortality due to silicosis.

Amorphous Silica, Inhalation. The available epidemiological studies in humans occupationally exposed to a-silica are inadequate to determine whether or not a-silica causes lung disease in humans. Studies reporting lung disease following occupational exposure to a-silica have known or suspected co-exposure to c-silica (reviewed by Merget et al. 2002; McLaughlin et al. 1997). Studies in workers exposed to synthetic a-silica with no known exposure to c-silica do not report lung disease (Choudat et al. 1990; Plunkett and Dewitt 1962; Taeger et al. 2016; Volk 1960; Wilson et al. 1979). A limited number of human studies have reported an increased risk of lung cancer or mesothelioma in industries with occupational exposure to a-silica; however, the usefulness of these studies is limited due to potential co-exposure to c-silica and lack of quantitative exposure data (Brooks et al. 1992; Checkoway et al. 1993; Le Blond et al. 2010; Rothschild and Mulvey 1982; Sinks et al. 1994; reviewed by McLaughlin et al. 1997; Merget et al. 2002). Available occupational

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exposure studies do not identify targets other than the respiratory system. Additional occupational exposure studies that have quantitative data on a-silica exposure and account for c-silica exposure would be helpful in defining the dose-response relationship between inhalation of a-silica and respiratory system toxicity. Additional studies also may identify other systemic targets for occupational exposure to a-silica.

Available animal data indicate that the primary target of chronic toxicity is the respiratory system following exposure to different synthetic a-silica polymorphs in multiple species. However, only limited data are available regarding the relative potency of polymorphs following chronic-duration exposure. Available data from chronic animal studies indicate that chronic inhalation exposure to a-silica can lead to various pulmonary effects in rats, guinea pigs, rabbits, and monkeys, including inflammation, hypertrophy, emphysema, early nodular fibrosis, and reduced lung function (Groth et al. 1981; Schepers 1959, 1962, 1981; Schepers et al. 1957b). However, a near-complete reversal of adverse effects was generally observed during a recovery period of 1–12 months. The lowest LOAEL values for precipitated, pyrogenic, and gel a-silica are, 6.9, 9.9, and 9.5 mg/m³, respectively; no NOAEL values were identified (Groth et al. 1981). Other effects observed in chronic inhalation studies included cardiac hypertension and hypertrophy in rabbits at ≥ 30 mg/m³ and cardiac hypertrophy in monkeys at 15 mg/m³ (Schepers 1959, 1962, 1981). Additional effects noted only in monkeys included hepatocellular hypertrophy and renal congestion with cloudy swelling of the convoluted tubules at 15 mg/m³ (Schepers 1962). No chronic studies evaluated natural a-silica or colloidal silica. Given the lack of a NOAEL value for respiratory effects following exposure to a-silica, well-designed chronic-duration inhalation toxicity studies with natural a-silica and multiple polymorphs of a-silica could provide more information regarding comparative potencies across a-silica forms and establish NOAEL values for respiratory effects.

Health Effects.

Respiratory. Data needs for c-silica and a-silica respiratory effects are discussed above under MRLs.

Renal

Crystalline Silica. A wide-spectrum of renal pathologies (called silicon nephropathy) have been associated with occupational exposure to c-silica, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, glomerulonephritis, and renal damage associated with

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autoimmune disorders (e.g., ANCA-associated vasculitis). Additional well-designed intermediate- and chronic-duration inhalation toxicity studies of c-silica would provide additional information regarding renal effects of inhaled c-silica and define the lower end of the exposure-response relationship. Oral exposure to c-silica is not associated with adverse renal effects.

Amorphous Silica. Few studies have been examined the potential a-silica exposure to produce adverse renal effects. Only one study in monkeys reported kidney effects (renal congestion and cloudy swelling) (Schepers 1962); however, these findings may be due to general compound toxicity rather than specific renal pathology. Other inhalation and oral exposure studies in animals did not identify adverse effects to the kidney. Any additional studies would be expected to confirm that the kidney is not a target for a-silica.

Immunological

Crystalline Silica. Numerous retrospective cohort and case-control studies have evaluated potential associations between c-silica exposure and a wide spectrum of autoimmune disorders, including systemic sclerosis (scleroderma), rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis (Bartunkova et al. 2006; Beaudreuil et al. 2005; Bovenzi et al. 1995, 2004; Brown et al. 1997; Burns et al. 1996; Calvert et al. 2003; Conrad et al. 1996; Cooper et al. 2010; Cowie 1987; Diot et al. 2002; Englert et al. 2000; Finckh et al. 2006; Gold et al. 2007; Gregorini et al. 1993; Hogan et al. 2001; Klockars et al. 1987; Lacey et al. 1997; Koskela et al. 1987b; Makol et al. 2011; Maitre et al. 2004; Marie et al. 2014; Nuyts et al. 1995; Rafnsson et al. 1998; Rihova et al. 2005; Rodnan et al. 1967; Rosenman and Zhu 1995; Rosenman et al. 1999; Silman and Jones 1992; Sluis-Cremer et al. 1985, 1986; Steenland and Brown 1995b; Steenland et al. 1992, 2001b; Stolt et al. 2005, 2010; Stratta et al. 2001b; Turner and Cherry 2000; Walsh 1999). However, exposure-response relationships for these effects are not well-defined. Additional occupational exposure studies providing quantitative exposure data may allow for identification of NOAEL and LOAEL values for autoimmune disorders.

Amorphous Silica. No studies evaluating immunological or lymphoreticular effects in humans following inhalation or oral exposure to a-silica were identified. No immune system toxicity was observed in rats following intermediate-duration exposure to pyrogenic a-silica at concentrations up to 30 mg/m³ (Reuzel et al. 1991) or in monkeys, rats, or guinea pigs following chronic exposure to precipitated, pyrogenic, or gel a-silica at concentrations up to 15 mg/m³ (Groth et al. 1981; Schepers 1962). Similarly, no immune system effects were observed in rats exposed to

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oral a-silica at doses of 500 mg/kg/day for 6 months or 100 mg/kg/day for 24 months (Lewinson et al. 1994). Given the limited data on a-silica and the immunotoxicity associated with c-silica, additional well-controlled occupational and animal studies would provide information regarding the potential for a-silica to produce autoimmune disorders.

Reproductive

Crystalline Silica. Epidemiological studies do not identify the reproductive system as a target for c-silica.

Amorphous Silica. No studies evaluating reproductive effects in humans following inhalation or oral exposure to a-silica were identified. No studies evaluation on reproductive function were identified following inhalation exposure to a-silica; however, no exposure-related changes in reproductive organs were observed in rats following intermediate exposure to pyrogenic a-silica at 30 mg/m³ (Reuzel et al. 1991) or in monkeys, rats, or guinea pigs following chronic exposure to precipitated, pyrogenic, or gel a-silica at concentrations up to 9.9 mg/m³ (Groth et al. 1981). No effects on reproductive performance, sexual maturation, estrous cyclicity, sperm parameters, or reproductive organ histology were observed in a 2-generation study in rats with exposure to precipitated a-silica at gavage doses up to 1,000 mg/kg/day (Wolterbeek et al. 2015). Additionally, no effects on reproductive performance or reproductive organ histology were observed in a 1-generation study in rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day (Lewinson et al. 1994). Results of oral studies indicate that reproductive effects of a-silica are probably not of concern; therefore, additional reproductive studies do not appear to be critical.

Developmental

Crystalline Silica. Epidemiological studies do not identify developmental effects in association with c-silica.

Amorphous Silica. No studies evaluating developmental effects in humans following inhalation or oral exposure to a-silica were identified. No studies evaluating developmental effects in animals following inhalation exposure. No developmental effects were observed in offspring of rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day in a 2-generation study (Wolterbeek et al. 2015) or pyrogenic a-silica at dietary doses of 500 mg/kg/day in a 1-generation study (Lewinson et al. 1994). Results of these studies indicate that developmental

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effects of a-silica are probably not of concern; therefore, additional developmental studies do not appear to be critical.

Cancer

Crystalline Silica. c-Silica is classified as a human lung carcinogen (IARC 2012; NIOSH 2002; NTP 2014). IARC (1997, 2012) acknowledged that some occupational exposure studies did not show an association between c-silica exposure and lung cancer, possibly due to the characteristics of c-silica in different occupational settings or other factors affecting its biological activity; in addition, other confounding factors and biases may have influenced study results (e.g., errors in estimating c-silica exposure levels, absence of or presence and severity of silicosis, adequate control of confounding from smoking, and unaccounted occupational co-exposures that may have contributed to lung cancer risk). (Brown 2009; Checkoway 2000; Checkoway and Franzblau 2000; Cox 2011; NIOSH 2002; Pelucchi et al. 2006; Smith et al. 1995; Soutar et al. 2000; Steenland and Ward 2014). Additional, well-controlled occupational exposure studies would provide important information regarding the exposure-response relationship for c-silica-induced lung cancer and the relationship between silicosis and lung cancer.

Amorphous Silica. Few studies have assessed the carcinogenicity of a-silica. Occupational exposure studies provide limited usefulness in examining the potential carcinogenicity of a-silica due to co-exposures to c-silica and lack of quantitative exposure data. Results of oral and inhalation bioassays in animals (Groth et al. 1981; Lesinson et al. 1994; Schepers 1981; Takizawa et al. 1988) did not indicate any neoplastic lesions following chronic exposure. Any additional studies are expected to confirm that a-silica is not carcinogenic.

Genotoxicity

Crystalline Silica. Results of numerous studies indicate that c-silica is a genotoxic agent in mammalian cells, with the ability to cause mutagenicity, clastogenicity, and DNA-damage. Chromosomal and DNA damage in peripheral lymphocytes and increased micronuclei formation in peripheral lymphocytes and nasal epithelial cells have been observed following occupational exposure to c-silica (Basaran et al. 2003; Demircigil et al. 2010; Sobti and Bhardwaj 1991); however, data are insufficient to determine the exposure-response relationship. Additional occupational exposure studies providing quantitative exposure data may allow for the determination of exposure-response relationships between inhaled c-silica and genotoxicity. *In vivo* studies in rodents exposed to c-silica by intratracheal instillation show DNA damage to lung

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epithelial cells (Knaapen et al. 2002; Seiler et al. 2001a, 2001b, 2001c). Results of *in vitro* studies also indicate that c-silica causes DNA damage, mutagenicity, and clastogenicity (Cakmak et al. 2004; Driscoll et al. 1997; Fanizza et al. 2007; Hart and Hesterberg 1998; Li et al. 2007; Msiska et al. 2010; Nagalakshmi et al. 1995; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000; Zhong et al. 1997b). Additional occupational exposure studies providing quantitative exposure data may allow for the determination of exposure-response relationships between inhaled c-silica and genotoxicity.

Amorphous Silica. Studies evaluating genotoxicity in humans following occupational exposure to a-silica were not identified. The few *in vivo* studies in animals were negative for mutations and induction of micronuclei (Johnston et al. 2000; Morita et al. 1997). However, results of *in vitro* studies show that a-silica can cause DNA and chromosomal damage, although conflicting results have been observed (Elias et al. 2006; Guidi et al. 2013; Liu et al. 1996a; Zhong et al. 1997b). Additional occupational exposure studies, *in vivo* animal studies, and *in vitro* studies would provide important information to clarify conflicting results and determine if a-silica is genotoxic under conditions of occupational exposure.

Mechanisms of Action. The ability of different c-silicas (tridymite, cristobalite, and quartz) to induce pulmonary fibrosis can vary. Although the underlying mechanism for this variability has not been firmly established, both surface and structural features of silica appear to play a critical role in the fibrogenic activity of silica (Altree-Williams and Sprogis 1982; Cox 2011; Donaldson and Borm 1998; Erdogdu and Hasirci 1998; Fujimura 2000; Guthrie 1995; IARC 2012; Leung et al. 2012; Mossman and Churg 1998; Murashov et al. 2006; Rimal et al. 2005; Shi et al. 2001). Additional studies on the role of surface and structural features of silica would enhance the understanding of differing fibrogenic potentials of different silica compounds. Fibrosis has not been associated with inhalation exposure to a-silica. However, additional information regarding the role of surface and structural features of a-silica would improve understanding of the mechanisms of a-silica to induce pulmonary effects.

Epidemiology and Human Dosimetry Studies. Numerous occupational exposure studies have been conducted on the effects of inhalation exposure to c-silica. Of special value in any ongoing or future occupational exposure studies is reliable exposure data, including quantitative data on the level and duration of exposure for c-silica and a-silica polymorphs.

Biomarkers of Exposure and Effect.

Exposure. Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that systemic distribution occurs in humans following inhalation exposure (Ibrahim et al. 2011). This suggests that urine may be an excretory pathway for c-silica absorbed from the respiratory tract. However, no studies examining the relationship between urinary silica and cumulative exposure were identified. Research examining the link between urinary silica and cumulative exposure may provide information that urinary silica serves as a biomarker for exposure.

Effect. Silicosis is a unique effect of exposure to c-silica. However, other than the signs and symptoms associated with silicosis, no other markers of effect have been identified. Several studies have examined the association between biomarkers of oxidative stress and inflammation in blood and urine in small numbers of silica-exposed workers and in laboratory animals. Markers examined include lactate dehydrogenase, alkaline phosphatase, tumor necrosis factors, interleukins, Clara cell proteins, and numerous proinflammatory cytokines (Aggarwal 2014; Altindag et al. 2003; Braz et al. 2014; Deb et al. 2012; Jiang et al. 2015; Sauni et al. 2012; Sellamuthu et al. 2011; Slavov et al. 2010; Wang et al. 2007). Additional research on the association between biomarkers and silica-exposed workers would be important to determine if such biomarkers could be used for early detection of silica-induced toxicity.

Absorption, Distribution, Metabolism, and Excretion.

Absorption. Quantitative estimates regarding absorption and pulmonary retention of c-silica and a-silica polymorphs are not available. Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that absorption occurs in humans following inhalation exposure (Ibrahim et al. 2011). Several studies have evaluated the pulmonary deposition and retention of c-silica and a-silica in the lung of animals (Borm and Tran 2002; Case et al. 1995; Davis 1986; Dobrevá et al. 1975; Donaldson and Borm 1998; Dufresne et al. 1998; Kelly and Lee 1990; Loosereewanich et al. 1995; Reuzel et al. 1991; Schepers 1981). Additional studies to determine quantitative estimates of pulmonary retention and clearance of c-silica and a-silica following inhalation exposure may provide important information regarding the toxic pulmonary load of silica compounds. Results of a single study evaluating the absorption of oral c-silica in rats indicates that silica was not absorbed (Gonzalez Huergo and Rojo Ortega 1991). Given the lack of quantitative information on pulmonary and oral absorption of c-silica and a-silica, well-controlled studies in humans and animals would provide important information to more fully describe the absorption of silica compounds.

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Distribution. Little information is available regarding extrapulmonary distribution of silica compounds. Occupational exposure studies indicate that inhaled c-silica distributes to the kidney, although quantitative information regarding distribution was not identified (Giles et al. 1978; Hauglustaine et al. 1980; Ibrahim et al. 2011; Saldanha et al. 1975). Studies in rats show distribution to blood, lymph nodes, thymus, kidney, liver, and spleen (Absher et al. 1992). No studies of distribution of silica compounds following oral exposure were identified. Given the lack of qualitative and quantitative information on distribution, well-controlled studies in humans and animals would provide important information to more fully describe the distribution of silica compounds.

Metabolism. Absorbed silica compounds are not metabolized. Additional studies on metabolism are not considered critical.

Excretion. Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that urine may be an excretory pathway for silica absorbed from the respiratory tract (Ibrahim et al. 2011). Ingested silica is excreted in the feces; however, there are no studies on urinary excretion of absorbed oral silica. Studies on urinary excretion of silica in workers and animals would provide information on relative contribution of excretory pathways and quantitative estimates on retention and excretion of silica.

Comparative Toxicokinetics. Very little is available on the post-absorptive kinetics of absorbed silica compounds. Silica is distributed to tissues outside of the respiratory tract. Additional studies on distribution and mechanisms of excretion would be useful to gain a better understanding of non-respiratory toxic effects.

Children's Susceptibility. No information regarding susceptibility of children to c-silica or a-silica has been identified. Silicosis and other adverse effects of silica exposure are strictly the result of occupational exposures that occur over a prolonged period (years). As such, children would not be exposed to silica at levels producing adverse effects. Therefore, studies on children's susceptibility are not considered critical.

Physical and Chemical Properties. The physical and chemical properties of the forms of silica are sufficiently well defined to allow an assessment of the environmental fate of these compounds (Haynes et al. 2014; IARC 1997). No additional data are needed at this time.

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Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2013, became available in October of 2014. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Because many forms of silica occur naturally (IARC 1997) and are widely used in industry, in the manufacture of household products, and in processing, packaging, and preserving food (IARC 2012), the potential for human exposure to silica through ingestion of food and water and inhalation of airborne particulates is substantial. Recent data on production, import/export, and use are available (USGS 2015). Information on disposal of silica is limited. In the United States, about 34% of silica glass containers were recycled in 2014 (USGS 2015). Additional information on disposal would be useful in assessing the potential for the release of and exposure to silica.

Environmental Fate. Silica is a solid that partitions to air as dust, water, soil, and plant material. Silica in the environment can undergo various weathering dissolutions or precipitations. Partitioning to various media is determined by the physical and chemical properties of the form of silica and the characteristics of the environmental matrix affecting its solubility (IARC 1997; Ning 2002). Silica is transported through the atmosphere primarily as a constituent of soil and other particulate matter (EPA 1996). Transformations are not expected to occur during transport of silica through the atmosphere. Information on the environmental fate of silica is sufficient to permit a general understanding of transport and transformation in all environmental media. No additional information is needed at this time.

Bioavailability from Environmental Media. Very limited information is available regarding absorption following oral or dermal exposure; however, these pathways of exposure are not expected to be significant. No additional information is needed at this time.

Food Chain Bioaccumulation. Diatoms are photosynthetic protists that take up dissolved silica from the water and precipitate opaline silica to form their cell wall (IARC 1997). α -Silica levels in diatoms ranges from <1% to approximately 50% by weight. Radiolarians and sponges also extract silica dissolved in water to form their shells. α -Silica has been found to accumulate in rice, millet, sugarcane, and wheat plants (Rabovsky 1995). No additional information is needed at this time.

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Exposure Levels in Environmental Media. Reliable monitoring data for the levels of silica in contaminated media at hazardous waste sites are needed so that the information obtained on levels of silica in the environment can be used in combination with the known body burden of silica to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Silica is ubiquitous in the environment. α -Silica has been found in samples from every geologic era and from every location around the globe (USGS 1992). Typical concentrations of silica in natural waters is 13 ppm for lakes, 3–15 ppm for major rivers, 1–10 ppm for seawater, 2–60 ppm for wells, and 50–300 ppm for wells in volcanic and oil fields (Ning 2002). Average ambient levels of silica with $<15 \mu\text{m}$ aerodynamic diameter in metropolitan areas of the United States generally have ranged between 0.001 and 0.003 mg/m^3 in most circumstances and are not expected to exceed 0.008 mg/m^3 annual average (EPA 1996). More recent studies on the ambient levels of silica are needed.

Exposure Levels in Humans. Data on nonoccupational exposures to all forms of silica are extremely limited. Limited analytical methods reported the analysis of silica in biological materials. All forms of silica are considered to be poorly soluble particles. Inhaled silica particles, not cleared by mucociliary escalators or coughing, are embedded and remain in the lung (Cox 2011). Additional information is necessary for assessing the need to conduct health studies on nonoccupationally exposed populations.

Exposures of Children. Limited analytical methods reported the analysis of silica in biological materials. More recent studies on the ambient levels of silica are needed. Data were not available on the intake of silica in food eaten by children and from their diet. Current information on whether children are different in their weight-adjusted intake of silica via oral, inhalation, and dermal exposures was not located. A study to determine this information would be useful.

6.3 Ongoing Studies

Ongoing research identified in the National Institute of Health (NIH) RePORTER (2015, 2019) database is summarized in see Table 6-1). The NIH RePORTER (2015, 2019) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.2. These studies are summarized in Table 6-1.

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Table 6-1. Ongoing Studies on Silica Compounds

Principal investigator	Study topic	Institution	Sponsor
Blanc, PD	Silicosis and rheumatoid arthritis risk in military personnel	Veterans Affairs Medical Center, San Francisco, California	Not identified
Bodduluri, H	Innate immune mechanisms regulating silicosis	University of Louisville, Louisville, Kentucky	National Institute of Allergy and Infectious Diseases
Chugh, YP	Physical and chemical characteristics of different particle size coal and quartz dusts from different unit operations; sampling data from the Interior Coal Basin mines from the Mine Safety and Health Administration and company dust data will be utilized to identify occupations and locations most exposed; evaluation of surface and wettability characteristics for different size fractions of coal and silica dusts generated during mining, haulage, and roof support operations	Southern Illinois University Carbondale	National Institute for Occupational Safety and Health
Downey, GP	Mechanism-of-action study in mouse fibroblasts	National Jewish Health, Denver, Colorado	National Institute of Environmental Health Sciences
Fattman, CL	Use of stem cells as therapy for silicotic lung disease using mice as the animal model	University of Pittsburgh at Pittsburgh, Pittsburgh, Pennsylvania	National Institute of Environmental Health Sciences
Holian, A	Mechanisms of c-silica-induced fibrosis examining the role of activated lung macrophages and natural killer (NK) lymphocytes	University of Montana, Missoula, Montana	National Institute of Environmental Health Sciences
Inman, K	Technical support for studies examining the role of environmental exposures of inhaled silica in autoimmunity in mice	Integrated Laboratory Systems, Research Triangle Park, North Carolina	National Institute of Environmental Health Sciences
Kelly, C	Mechanism of tissue-specific fibrosis in autoimmune-prone mice	Integrated Laboratory Systems, Inc., Research Triangle Park, North Carolina	National Institute of Environmental Health Sciences
Larue, AC	The potential of circulating fibroblast precursor as a biomarker of pulmonary fibrosis using a silica mouse model	Ralph H. Johnson VA Medical Center, Charleston, South Carolina	Veteran's Administration

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Principal investigator	Study topic	Institution	Sponsor
Laskin, DL	Mechanism examining the role of caveolin-1 and TNF α in silica-induced toxicity	The State University of New Jersey at Rutgers, Rutgers, New Jersey	National Cancer Institute
Migliaccio, CT	Mechanism of multiple cell types and soluble factors in silicosis	University of Montana, Missoula, Montana	National Center for Research Resources
Miller, F	Evaluation of exposures to items including silica to assess relationships and development of systemic autoimmune diseases	National Institute of Environmental Health Sciences	National Institute of Environmental Health Sciences
Ortiz, LA	Role of tumor necrosis factor receptor-1 phosphorylation on silica-induced lung injury	University of Pittsburgh at Pittsburg, Pittsburg, Pennsylvania	National Institute of Environmental Health Sciences
Ortiz, LA	Mechanisms of bone marrow derived mesenchymal stem cells to employ microvesicles as a means to deliver peptides, miRNAs, and mitochondria to reprogram the innate immunity and ameliorate silicosis	University of Pittsburgh at Pittsburg, Pittsburg, Pennsylvania	National Heart, Lung, and Blood Institute
Pollard, KM	Characterization of silica-induced immunological responses leading to autoimmunity in mice	Scripps Research Institute, La Jolla, California	National Institute of Environmental Health Sciences

Source: RePORTER 2015, 2019.