CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Silica is ubiquitous in the environment, with over 95% of the earth's crust made of minerals containing silica (Uhrlandt 2006). Silica exists in two forms: crystalline (c-silica) and amorphous (or non-crystalline; a-silica). At least a trace amount of c-silica, in the form of quartz, is present in all soils. Silica is naturally released into the environment through the weathering of rocks, volcanic activity, and biogenic sources.

c-Silica and a-silica are not single entities, each having several forms (polymorphs) with different surface chemistry characteristics. For a single polymorph, surface characteristics may vary due to processing and particle aging, even for polymorphs within the same silica industry. The most common polymorphs of naturally occurring c-silica include quartz, cristobalite, and tridymite (NIOSH 2002). a-Silica exists in natural forms that often contain various amounts of c-silica (diatomite, calcined, flux calcined, biogenic silica fibers, opal, vitreous silica) and in synthetic forms that are not contaminated with c-silica (pyrogenic, precipitated, gel, colloidal) (Fruijtier-Polloth 2012; IARC 1997). Vitreous silica can also be produced intentionally as a commercial product or unintentionally as a byproduct during the manufacture of ferrosilicon and silicon (Arts et al. 2007; Fruijtier-Polloth 2012; IARC 1997; Smith 2006). Similarly, a-silica fume can be produced unintentionally as a byproduct during the manufacture of ferrosilicon and silicon; the resulting product can then be used in some manufacturing processes (Arts et al. 2007; Florke et al. 2008; Fruijtier-Polloth 2012). Unlike intentionally produced synthetic forms of a-silica, a-silica byproducts are produced in an uncontrolled manner and may contain varying amounts of c-silica. Synthetic a-silica compounds typically exist as aggregates, with particle sizes in the respirable range (<10 μm) (Fruijtier-Polloth 2012, 2016; Merget et al. 2002; IARC 1997; Waddell et al. 2006). However, isolated synthetic a-silica particles may exist as nanoparticles (1–100 nm) in colloidal dispersions (Fruijtier-Polloth 2012, 2016).

In general, silica is considered poorly water soluble and chemically unreactive in the environment (EPA 1991; IARC 1997). Both c- and a- forms of silica have surfaces composed of siloxane (covalently bonded silicon and oxygen; Si-O-Si) and silanol groups (Si-OH) (Rimola et al. 2013; Zhuravlev 2000). Exposure to water will break silicon-oxygen bonds on the surface of silica to form silanols. c-Silica surfaces tend to have more order, although some c-silica is found with an outer layer of a-silica. a-Silica may contain a c-silica component from exposure to high temperatures and pressures (e.g., flux calcination). Thus, for a

single polymorph of c- or a-silica, surface chemistry of the compound may vary, depending upon production method and degree of hydration. The water solubility of silica has some variability due to differences in trace metal impurities, hydration, temperature, and particle size. Solubility is lower for c-silica polymorphs than for a-silica, and anhydrous a-silica dissolves less rapidly than hydrated a-silica (IARC 1997). Silica particles may be transported by wind or water currents as part of the biogeochemical silica cycle. As part of the biogeochemical silica cycle, silica deposits settle out of water into sediment.

Human exposure to c-silica is known to occur in industrial and occupational settings (NTP 2014). c-Silica is recognized as an important occupational inhalation hazard (EPA 1996). The general population is exposed to silica through air, indoor dust, food, water, soil, and various consumer products. Both c-silica and a-silica are found in many commercial products (e.g., bricks, mortar, plaster, caulk, granite and engineered stone kitchen counter tops, roofing granules, wallboard, concrete cleansers, skin care products and soaps, art clays and glazes, talcum powder) (NTP 2009). The primary route of exposure to c-silica in the general (non-occupational) population is thought to be via inhalation of c-silica during the use of commercial products containing quartz (IARC 2012). Silica sands and dusts are commonly found in air and a-silica and c-silica can be air contaminants from emission of fly ash from power stations and various manufacturing facilities (IARC 1997). Industrial emissions, forest fires, crop burning, and wind erosion of soil may spread both a-silica and c-silica particles. Exposure to silica is also expected to occur for the general public through the diet. a-Silica compounds are used as pesticides for crops and are used near food handling and preparation areas (EPA 1991). a-Silica compounds are used in food packaging, cosmetics (e.g., toothpaste), and pharmaceutical agents, and are approved food additives (FDA 2015a, 2015b; Fruijtier-Polloth 2012, 2016). a-Silica accumulates in some plants and crops including rice, millet, sugarcane, and wheat (Rabovsky 1995). Although quantitative data are not available, water containing c-silica and a-silica (e.g., diatomite fragments and quartz particles) is a potential source of exposure for the general population.

1.2 SUMMARY OF HEALTH EFFECTS

Throughout this toxicological profile, the term *c-silica* refers to crystalline silica; non-crystalline amorphous silica is referred to as *a-silica*. As noted above (Section 1.1), surface chemistry of a single polymorph of c-silica or a-silica may vary depending upon production method, degree of hydration, and aging. Thus, particle surface chemistry resulting in differences in chemical reactivity may contribute, along with other factors, to differences observed between studies (Fubini et al. 1995; Rimola et al. 2013; Turci et al. 2016; Zhuravlev 2000).

1. RELEVANCE TO PUBLIC HEALTH

The exposure route of concern for c-silica and a-silica compounds is inhalation. Effects of inhaled c-silica are strictly associated with occupational exposure to particles that are of respirable size (<10 µm). Adverse effects of inhaled c-silica are not observed from incidental exposure to low levels of c-silica in the environment (e.g., at beaches) or from exposure particles that exceed the respirable size range (Beckett et al. 1997; Steenland and Ward 2014). Note that studies evaluating silica compounds with a mean particle size in the nanoparticle range (≤100 nm) are not included in this profile because toxicokinetics and toxicodynamics of nanoparticles can be substantially different from larger respirable particles (Oberdorster 2010).

Few studies on oral exposure to c-silica were identified. Available studies in laboratory animals, as reviewed in Chapter 2, do not identify adverse effects associated with oral exposure. Given the ubiquitous nature of c-silica in the environment, it is assumed that incidental oral exposure of humans commonly occurs; however, no reports of adverse effects associated with incidental oral exposure to c-silica in the environment were identified. For a-silica, results of oral exposure studies in animals available in the published literature (reviewed in pertinent sections of Chapter 2) do not identify adverse effects associated with exposure. In addition, results of numerous unpublished oral exposure studies in animals on synthetic a-silica are reported by the Organization for Economic Co-operation and Development (OECD 2016) and the European Chemicals Agency (ECHA 2019). Based on the information presented in the OECD and ECHA documents, no adverse effects were associated with oral a-silica exposure in these studies, with exposure durations ranging from acute to chronic duration. Note that synthetic a-silica compounds are used in food packaging, cosmetics (e.g., toothpaste), and pharmaceutical agents, and are approved food additives (FDA 2015a, 2015b; Fruijtier-Polloth 2012, 2016); therefore, incidental exposure of the general population to synthetic a-silica is expected to occur.

No association between dermal exposure and adverse effects for a-silica or c-silica in humans or animals has been reported in the available published literature or in the unpublished studies reviewed by the OECD (2016) or ECHA (2019).

Health Effects of Inhaled Crystalline Silica. To date, exposures to c-silica at levels that produce adverse health effects have only been reported in workers who have been exposed by inhalation for a prolonged period of time in silica industries. Health effects that have been associated with occupational exposure to c-silica are silicosis (a progressive, fibrotic lung disease), chronic obstructive pulmonary disease (COPD), lung cancer, renal toxicity, increased risk of tuberculosis, and autoimmune diseases. Of these, silicosis

and lung cancer pose the greatest concern to human health. Under most exposure conditions, silicosis occurs from chronic exposure. However, intermediate-duration exposure to high levels (not defined) of c-silica has been associated with the development of silicosis, although this is not common. It is important to note that these health outcomes have not been associated with exposures to ambient air levels of c-silica (Beckett et al. 1997; Mossman and Churg 1998; Steenland and Ward 2014). Renal and autoimmune outcomes have not been studied as extensively as silicosis and lung cancer.

Respiratory effects. Silicosis is a progressive, irreversible, fibrotic lung disease that can occur in association with inhalation and pulmonary deposition of respirable dust containing c-silica. The association between occupational exposure to inhaled c-silica and development of this severe, debilitating lung disease is well-established and has been recognized since ancient times. Silicosis does not result from inhalation of any other substance, including a-silica. Silicosis is not a single disease entity, but is classified as different types (simple silicosis, progressive massive fibrosis [PMF], acute silicosis, and accelerated silicosis). Silicosis can result in death due to respiratory failure. Cumulative c-silica exposure, expressed as mg/m^3-year, is the most important factor in the development of silicosis. Time from first exposure to onset of disease varies inversely with cumulative exposure and may be as short as a few weeks for acute silicosis or as long as 20 or more years for simple silicosis and PMF. Due to the long latency period, silicosis may not be diagnosed until after exposure has ended. Disease severity continues to slowly increase over decades even after exposure has been discontinued, possibly due to c-silica dust that is retained in the lungs (Greenberg et al. 2007).

The current number of silicosis cases in the United States is not known. Based on confirmed diagnoses of silicosis in Michigan and national data on silicosis deaths, Rosenman et al. (2003) estimated that during the period of 1987–1997, approximately 3,600–7,300 new silicosis cases were diagnosed yearly in the United States. Reported risk estimates for silicosis in occupational exposure studies vary, with many factors potentially influencing study outcome, including study design (inclusion of decedents, length of follow-up period, frequency of health assessments, adjustment for smoking), and c-silica surface characteristics. These likely factors contribute to the wide range of reported incidences of silicosis (<10% to as high as approximately 80%) (Chuchyard et al. 2004; Collins et al. 2005; Kreiss and Zhen 1996). Based on data reported by the National Institute for Occupational Safety and Health (NIOSH) in 1994, 13,744 deaths with silicosis as a possible contributor (mentioned in the death certificate) occurred in the United States during the period 1968–1990 (Castranova and Vallyathan 2000; NIOSH 1994). Silicosis mortality trends have shown a marked decline over the past 50 years due to improved industrial hygiene standards and more stringent regulatory standards and guidelines (Bang et al. 2008, 2015). However,

silicosis deaths in younger adults (ages 15–44 years) have not declined since 1995, which may reflect more recent, intense exposures, such as those associated with construction and abrasive blasting industries (CDC 1998a, 1998b; Mazurek and Attfield 2008).

Several occupational studies have demonstrated exposure-response relationships for silicosis and mortality due to silicosis. However, a no-observed-adverse-effect level (NOAEL) for silicosis has not been defined, with silicosis and death due to silicosis observed for the lowest estimated cumulative exposure ranges reported. For the lowest estimated cumulative exposure range reported in the available literature (0–0.2 mg/m^3-year), silicosis was observed in 5 of 3,330 gold miners (Steenland and Brown 1995a). At the estimated cumulative exposure range of 0.1–1.23 mg/m^3-year, death due to silicosis was observed in 2,857 of 74,040 mining and pottery workers in China (Chen et al. 2012). In other occupational studies, cumulative exposure levels associated with silicosis and silicosis-related death are higher.

Renal effects. 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 autoimmune disorders (e.g., anti-neutrophil cytoplasm antibody [ANCA]-associated vasculitis). However, associations have not been found in all studies. Relative to silicosis, the incidence of renal disease is very low in silica-exposed cohorts (<1 versus <10–80%). Results of a pooled analysis show that the risk of renal disease and mortality due to renal disease increased with cumulative exposure (Steenland et al. 2002a). Comparison of exposure-response data for renal effects and silicosis shows that renal toxicity typically occurs at higher cumulative exposure levels than silicosis.

Immunological effects. Exposure to respirable c-silica has been associated with increased risks of a wide spectrum of autoimmune disorders, including systemic sclerosis (scleroderma), rheumatoid arthritis, systemic lupus erythematosus, ANCA-associated vasculitis, and sarcoidosis. Similar to renal effects, the incidence of autoimmune disorders is low compared to silicosis, and associations have not been observed in all studies (Brown et al. 1997; Calvert et al. 2003; Gold et al. 2007; Makol et al. 2011; Rosenman et al. 1999; Walsh 1999). Data for each specific disease are inadequate to determine exposure-response relationships.

Lung cancer. Numerous epidemiological studies have evaluated associations between silica exposure and lung cancer. Compared to other occupational lung carcinogens, such as asbestos, the reported association

between c-silica exposure and lung cancer is low, requiring large study populations to achieve adequate power to detect and quantify any such association. Results of pooled- and meta-analyses, which provide the strongest support for the carcinogenicity of c-silica in the lung, show increased risks of lung cancer in c-silica workers, with risks exhibiting dependence upon cumulative exposure (Finkelstein 2000; Lacasse et al. 2009; Steenland 2005; Steenland et al. 2001a). Results of a cohort study of over 30,000 workers in China indicate that exposure to c-silica is associated with lung cancer in the absence of silicosis (Liu et al. 2013). Smoking, as in all studies of potential lung carcinogens, could be a confounding factor in studies examining the relationship between c-silica exposure and lung cancer (Hessel et al. 2000). However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking (Steenland et al. 2001a).

The Department of Health and Human Services classified c-silica (respirable size) as a Group 1 (definite) human lung carcinogen. The International Agency for Research on Cancer (IARC 2012) and NIOSH (2002) also have classified c-silica (respirable size) as a Group 1 (definite) human lung carcinogen. 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 carcinogenic potential; in addition, other confounding factors and biases may have influenced study results (e.g., errors in estimating c-silica exposure levels, absence [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). NIOSH (2002) also concluded that c-silica (respirable size) is a human carcinogen.

Health Effects of Inhaled Amorphous Silica. Relative to the large number of occupational studies on c-silica, fewer studies have evaluated the effects of inhaled a-silica in humans. Data from occupational exposure studies are insufficient to determine whether or not a-silica is associated with lung disease in humans because exposure in most studies includes a mixture of a-silica and c-silica. However, silicosis has not been observed in epidemiological studies in workers with long-term exposure to a-silica with no known exposure to c-silica (Choudat et al. 1990; Plunkett and Dewitt 1962; Taeger et al. 2016; Volk 1960; Wilson et al. 1979). Numerous occupational studies in the 1930s–1980s report an increased incidence of pneumoconiosis in diatomaceous earth workers exposed to a-silica; however, interpretation of results is complicated due to co-exposures to c-silica (Beskow 1978; Caldwell 1958; Cooper and Jacobson 1977; Cooper and Sargent 1984; Dutra 1965; Harber et al. 1998; Legge and Rosencrantz 1932; Motley 1960; Motley et al. 1956; Smart and Anderson 1952; Vigliani and Mottura 1948).

Results of animal studies on synthetic a-silica polymorphs indicate that inhalation exposure to a-silica is associated with pulmonary toxicity, including inflammation, cellular infiltrates, reversible fibrosis, and reduced lung function, following acute-, intermediate-, and chronic-duration exposure (Arts et al. 2007; Groth et al. 1981; Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Schepers 1959, 1962, 1981; Schepers et al. 1957a, 1957b, 1957c; Tebbens et al. 1957; Warheit et al. 1991, 1995). However, in contrast to c-silica, progressive fibrosis was not observed and most effects were reversible. Results of a study examining the effects of a 5-day inhalation exposure of rats to a-silica polymorphs yield NOAEL and lowest-observed-adverse-effect level (LOAEL) values for bronchial hypertrophy and cellular infiltrates of 1 and 5 mg/m^3, respectively (Arts et al. 2007). Similar pulmonary effects have been reported in animals following intermediate- and chronic-duration inhalation exposure; however, NOAEL values were not identified (Groth et al. 1981; Reuzel et al. 1991; Warheit et al. 1991, 1995).

Other than pulmonary effects, no other effects are clearly associated with inhaled a-silica.

1.3 MINIMAL RISK LEVELS (MRLs)

Crystalline Silica, Inhalation. As reviewed in Section 1.2, epidemiological studies of occupational populations show that silicosis occurs at the lowest estimated cumulative exposure levels reported. Silicosis is a serious adverse effect that has the potential to result in death due to respiratory failure or lung cancer. Given the serious nature of silicosis and the uncertainties associated with identification of a no-effect level, no MRLs were derived for inhaled c-silica for any exposure duration, as summarized in Table 1-1.

Table 1-1. Minimal Risk Levels (MRLs) for c-Silica[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

Crystalline Silica, Oral. Studies on oral exposure to c-silica do not identify critical target organs. Therefore, oral MRLs for c-silica have not been derived for any exposure duration, as summarized in Table 1-1.

Amorphous Silica Inhalation. As noted above (Health Effects of Amorphous Silica), results of the animal studies provide evidence that toxicological potency for respiratory effects can differ between different a-silica polymorphs. Given the potentially important role of surface chemistry characteristics in the toxicological potency of silica compounds, there is considerable uncertainty regarding identification of NOAEL or LOAEL values that could serve as the basis of development of inhalation MRLs, as values based on a single a-silica polymorph may not apply to all forms of a-silica. Therefore, inhalation MRLs for a-silica have not been developed for any exposure duration, as summarized in Table 1-2.

Table 1-2. Minimal Risk Levels (MRLs) for a-Silica[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

Amorphous Silica Oral. Studies on oral exposure to a-silica do not identify critical target organs. Therefore, oral MRLs for a-silica have not been derived for any exposure duration, as summarized in Table 1-2.