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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO SILICA IN THE UNITED STATES

Silica occurs naturally in crystalline and amorphous (or non-crystalline) forms, referred to as c-silica and a-silica, respectively. In general, silica is considered poorly water soluble and chemically unreactive in the environment. 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). Exposure to water will break silicon-oxygen bonds on the surface of silica to form silanols. In general, c-silica surfaces tend to have more order, although some c-silica is found with an outer layer of a-silica. a-Silica contains 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. 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.

Silica is ubiquitous; over 95% of the earth’s crust is made of minerals containing silica and c-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 (e.g., diatoms). Human activities such as mining and farming also result in the release of silica into the environment. Silica levels in environmental media vary depending upon the location and sampling site. Local meteorological conditions, such as wind and rain, especially in deserts and areas near recent volcanic eruptions and mine dumps, are expected to influence the location and spread of silica-containing dust. Remote continental air has a background gravimetric airborne dust concentration of 0.04 mg/m³ with ≥10% c-silica content. In urban areas across the United States, the measured mean 24-hour average ambient c-silica concentration ranged from 0.0009 to 0.008 mg/m³ for particles in the size range of 2.5–15 µm (aerodynamic diameter). Dissolved silica concentrations of natural waters are 13 ppm for lakes, 3–15 ppm for major rivers, 1–10 ppm for sea water, 2–60 ppm for wells, and 50–300 ppm for wells in volcanic fields or oil fields.

Human exposure to c-silica is known to occur in industrial and occupational settings. c-Silica is recognized as an important occupational inhalation hazard. 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). Inhalation of c-silica during the use of commercial products containing quartz is expected to be the predominant, non-occupational silica exposure route. Silica is also a common air contaminant. 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. a-Silica is used in food packaging, and in food, cosmetics, and pharmaceuticals as anticaking agents or carriers. a-Silica accumulates in some plants and crops including rice, millet, sugarcane, and wheat. Although quantitative data are not available, water containing diatomite fragments and quartz particles is a potential source of exposure for the general population.

All forms of silica are considered to be poorly soluble particles. There are limited analytical methods reported for the analysis of silica in biological materials. Very limited information is available regarding absorption of silica following dermal or oral contact; however, these pathways of exposure are not expected to be significant. Inhaled silica particles, not cleared by mucociliary escalators or coughing, are embedded and remain in the lung.

### 2.2 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. Note that due to significant differences in toxicokinetics of ultrafine and nanoparticles compared to larger respirable particles, silica nanoparticles are not considered in this profile.

c-Silica and a-silica are not single entities. Each exists in several forms (polymorphs) with different surface chemistry characteristics. For a single polymorph (e.g., quartz, cristobalite), surface characteristics may vary due to processing and particle aging, even for polymorphs within the same silica industry. Biological activity (potency) of both c-silica and a-silica is affected by particle surface chemistry. These differences in surface chemistry may, in part, play a role in differences observed for exposure-response relationships and inconsistent results for some health effects.
The exposure route of concern for c-silica and a-silica compounds is inhalation. Adverse health effects of inhalation exposure to c-silica and a-silica have been observed in studies of occupational exposure to particles that are of respirable size (<10 µm). Respirable particles of c-silica, which are deposited throughout the alveolar region of the lung and distributed to associated lymph tissue, produce a cascade of effects that result in the development of silicosis, a progressive, irreversible, fibrotic lung disease. It has been hypothesized that the severity of silicosis is related to the c-silica particle burden in the lung. No known adverse effects occur from exposure to particles that exceed the respirable size range or from incidental exposure to low levels of c-silica in the environment (e.g., at beaches). Regarding oral exposure to c-silica, available data in humans and laboratory animals are not sufficient to demonstrate an association for any adverse effect outcome. No information on the effects of oral a-silica in humans was identified, and very few studies evaluating adverse effects of oral a-silica in animals have been conducted. Available animal studies either do not identify adverse effects at the doses tested or do not provide sufficient data to determine the toxicological significance of observed effects (e.g., changes in organ weights in the absence of histopathological changes). No association between dermal exposure and adverse effects has been reported.

**Health Effects of Crystalline Silica**

**Silicosis Morbidity and Mortality:** Health effects associated with occupational exposure to c-silica are silicosis (a progressive, fibrotic lung 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.

Silicosis is a progressive, irreversible, fibrotic lung disease resulting from inhalation and pulmonary deposition of respirable dust containing c-silica. The causal relationship between inhalation of 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). All types of silicosis can result in death due to respiratory failure. Cumulative c-silica exposure, expressed as mg/m³-year, is the most important factor in the development of silicosis. Cumulative exposures typically are reported as stratified ranges or as the median of stratified ranges. 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.

The current number of silicosis cases in the United States is not known; however, it has been 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%). In the United States, 13,744 deaths were attributed to silicosis from 1968 to 1990 and 4,313 deaths were attributed to silicosis from 1979 to 1990. 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. 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.

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 cumulative exposure ranges reported. For the lowest cumulative exposure range reported in the available literature (0–0.2 mg/m³-year), silicosis was observed in 5 of 3,330 gold miners. At the cumulative exposure range of 0.1–1.23 mg/m³-year, death due to silicosis was observed in 2,857 of 74,040 mining and pottery workers in China. Cumulative exposure levels reported in other occupational studies have been higher.

**Lung Cancer:** The International Agency for Research on Cancer, the National Institute of Occupational Safety and Health, and the National Toxicology Program 13th Report on Carcinogens have classified c-silica (respirable size) as a Group 1 (definite) human lung carcinogen. IARC 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 [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).
Compared to other occupational lung carcinogens, such as asbestos, the occupational risk of c-silica-induced lung cancer is low, requiring large study populations to achieve adequate power to detect and quantify c-silica-related cancer risk. 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. Results of a cohort study of over 30,000 workers in China indicate that c-silica can induce lung cancer in the absence of silicosis. 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. However, results of a pooled analysis of over 65,000 workers show that smoking was not a confounder in studies with data on smoking.

*Other Adverse Health Effects of Inhaled Crystalline Silica:* Occupational exposure to respirable c-silica is also associated with adverse effects to the kidney and autoimmune diseases. However, these effects have been studied much less than silicosis, and study results have not been consistent regarding associations between c-silica exposure and increased risks. Unlike silicosis, no renal or autoimmune diseases are uniquely associated with exposure to c-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 autoimmune disorders (e.g., anti-neutrophil cytoplasm antibody [ANCA]-associated vasculitis). 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. Comparison of exposure-response data for renal effects and silicosis shows that renal toxicity typically occurs at higher cumulative exposure levels than silicosis.

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. Data for each specific disease are inadequate to determine exposure-response relationships.

*Health Effects of Amorphous Silica.* Relative to the abundance of data on c-silica, few studies have evaluated the effects of inhaled a-silica. Data are insufficient to determine whether or not a-silica causes
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lung disease in humans; 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. 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.

Results of animal studies indicate that inhalation exposure to a-silica causes pulmonary toxicity, including inflammation, cellular infiltrates, reversible fibrosis, and reduced lung function, following acute-, intermediate-, and chronic-duration exposure. 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/m³, respectively. Similar pulmonary effects have been reported in animals following intermediate- and chronic-duration inhalation exposure; however, NOAEL values were not identified.

Other than pulmonary effects, no other effects associated with inhaled a-silica have been established.

2.3 MINIMAL RISK LEVELS (MRLs)

**Crystalline Silica.** Effects on the respiratory system are the most sensitive effects of inhaled c-silica. However, identification of a no-effect or threshold level for silicosis is highly uncertain due to several factors. For example, in one study for the lowest reported cumulative exposure range of 0–0.2 mg/m³-year, silicosis was observed (Steenland and Brown 1995a). Cumulative exposure ranges identifying a no-effect level for silicosis have not been identified. In addition, the long latency period between exposure and time to onset of symptoms or diagnosis of silicosis could affect identification of a no-effect level for silicosis if follow-up periods are not sufficiently long. Exclusion of decedents and poor or inadequate health records also contribute uncertainty of risks for silicosis. Furthermore, due to the variable surface chemistry characteristics, the biological potency of c-silica can vary between and among c-silica polymorphs. Therefore, even if a no-effect level could be identified for a particular occupational cohort, that level may cause silicosis in a different occupational cohort due to differences in surface chemistry of c-silica.

LOAEL values for silicosis have been identified in several studies; however, silicosis is a serious adverse effect that has the potential to cause 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.

Available data for oral exposure to c-silica are insufficient to derive oral MRLs for any exposure duration.

**Amorphous Silica.** Relative to the abundance of data on c-silica, few studies have evaluated the effects of inhaled a-silica. Data are insufficient to determine whether or not a-silica causes lung disease in humans; 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; 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; Legge and Rosencrantz 1932; Smart and Anderson 1952; Vigliani and Mottura 1948).

As reviewed below, available data from animal studies indicate that inhalation exposure to a-silica causes pulmonary toxicity, including pulmonary inflammation, increases in cellular infiltrates, reversible fibrosis, reduced lung function, and respiratory distress (Arts et al. 2007; Groth et al. 1981; Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Warheit et al. 1991, 1995). Pulmonary effects observed following exposure to a-silica are reversible and progressive fibrosis is not observed, in contrast to the pulmonary effects of c-silica. Results of animal studies also indicate that different polymorphs of a-silica have different toxicological potencies (Arts et al. 2007; Warheit et al. 1991, 1995). Other than pulmonary effects, no other effects associated with inhaled a-silica have been established.

**Acute-Duration Exposure:** Arts et al. (2007) examined the effects of a 5-day inhalation exposure of rats to three types of a-silica polymorphs: silica gel (Syloid 74), precipitated silica (Zeosil 45), and pyrogenic silica (Cab-O-Sil M5). After the final day of exposure, microscopic examination of lung tissue showed differences between the three polymorphs. For silica gel, NOAEL and LOAEL values of 5 and 25 mg/m³, respectively, were identified for accumulation of alveolar macrophages in male rats (females not examined). For precipitated silica, NOAEL and LOAEL values for alveolar granulocyte infiltrates were 1 and 5 mg/m³, respectively, in males and 5 and 25 mg/m³, respectively, in females. For pyrogenic silica, NOAEL and LOAEL values for accumulation of alveolar macrophages were 1 and 5 mg/m³, respectively, in male rats (females not examined). The incidence of bronchial/bronchiolar hypertrophy was increased in rats exposed to precipitated and pyrogenic silica at 25 mg/m³, although the incidence of
hypertrophy was not increased for silica gel. Warheit et al. (1991, 1995) observed increased neutrophils in bronchoalveolar lavage fluid of rats exposed to colloidal silica (Ludox) and precipitated silica (Zeofree 80) for 2 weeks. The NOAEL and LOAEL values for colloidal silica were 10.1 and 50.5 mg/m³, respectively. The LOAEL value for precipitated silica was 10 mg/m³; a NOAEL was not identified. However, NOAEL and LOAEL values for the Arts et al. (2007) and Warheit et al. (1991, 1995) studies are not directly comparable, as microscopic examination of lung tissue was not conducted in the Warheit et al. (1991, 1995) studies. Respiratory distress, a serious adverse effect, was observed in rats exposed for 2 weeks to three a-silica polymorphs: fumed hydrophilic silica (Aerosil 200), fumed hydrophobic silica (Aerosil R 974), and precipitated hydrophobic silica (Sipernat 22S) (Reuzel et al. 1991). For all three polymorphs, respiratory distress was observed at the lowest concentration tested, with LOAEL values of 17, 31, and 46 mg/m³ for fumed hydrophilic silica, fumed hydrophobic silica, and precipitated hydrophobic silica, respectively. However, relative potency of the different polymorphs cannot be determined from this study, as respiratory effects were observed at the lowest tested concentration for each polymorph. Although all a-silica polymorphs have not been evaluated for acute respiratory toxicity, results of acute inhalation studies in rats indicate that the biological activity of a-silica varies between polymorphs.

Intermediate-Duration Exposure: Results of intermediate-duration inhalation studies show a wide range of toxicological potencies for a-silica polymorphs (Johnston et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Warheit et al. 1991, 1995). Respiratory effects, including fibrosis, increased cellularity, inflammation, accumulation/aggregation of alveolar macrophages (granulomas), and increased collagen content were observed in rats exposed to ≥1 mg/m³ of fumed hydrophilic silica (Aerosil 200) for 13 weeks (Reuzel et al. 1991); a NOAEL was not identified. Similar effects, except fibrosis, were also observed following exposure to fumed hydrophobic silica (Aerosil R974) and precipitated silica (Sipernat 22S) at 30 mg/m³; no other exposure levels were tested (Reuzel et al. 1991). In contrast, NOAEL and LOAEL values of 10 and 50 mg/m³, respectively, were identified for less serious respiratory effects (inflammation, hyperplasia, increased neutrophils in bronchoalveolar lavage fluid) following a 4-week exposure to colloidal silica (Ludox) (Johnston et al. 2000; Lee and Kelly 1992). Additional information on intermediate-duration inhalation exposure is provided in Section 3.2.1.2.

Chronic-Duration Exposure: Studies in monkeys, rats, guinea pigs, and rabbits also show adverse respiratory effects, including fibrosis, reduced lung function, and macrophage accumulation, following chronic-duration inhalation exposure to several a-silica polymorphs (Groth et al. 1981; Schepers 1981) (see Section 3.2.1.2 for additional information). However, comparison of potency between polymorphs
cannot be conducted as studies only evaluated single exposure levels. Furthermore, as only single
exposure levels were evaluated, data are not suitable to serve as the basis for a chronic-duration inhalation
MRL for a-silica.

Conclusions: The biological activity of silica compounds varies based upon surface chemistry of the
compound (Donaldson and Borm 1998; Greenberg et al. 2007; Guthrie 1995; Mossman and Churg 1998;
Mossman and Glenn 2013). Even for a single polymorph, surface chemistry may vary depending upon
production method, degree of hydration, and aging (Fubini et al. 1995; Rimola et al. 2013; Zhuravlev
2000). Numerous polymorphs of a-silica exist, each with different surface chemistry properties and,
therefore, the potential for different biological potencies. Although analytical techniques exist to
distinguish between a-silica polymorphs, most are too sophisticated for routine measurements (IARC
1997). Therefore, exposures typically are reported as a-silica, rather than as specific a-silica polymorphs.

As reviewed above, results of the animal studies provide evidence that toxicological potency for
respiratory effects can differ between different a-silica polymorphs. Given the important role of surface
chemistry 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 discussed in Section 2.2, no information on the effects of oral a-silica in humans was identified, and
available animal studies either do not identify adverse effects at the doses tested or do not provide
sufficient data to determine the toxicological significance of observed effects. Therefore, available data
for a-silica are insufficient to derive oral MRLs for a-silica for any exposure duration.