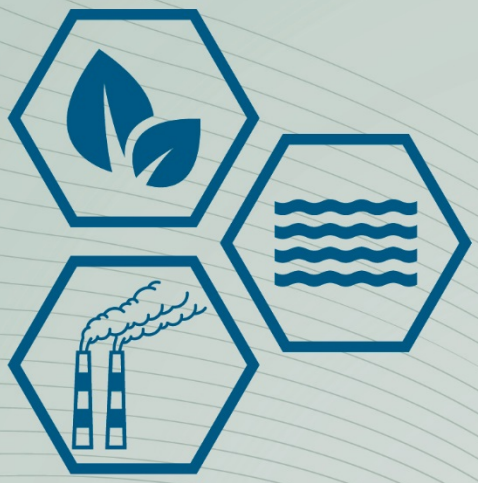

Toxicological Profile for Silica

September 2019

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

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The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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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.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of silica. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints.

Summaries of the human observational studies are presented in Tables 2-4 through 2-18. Animal inhalation studies are presented in Table 2-1 and Figure 2-1, and animal oral studies are presented in Table 2-2 and Figure 2-2 for crystalline silica and Table 2-3 and Figure 2-3 for amorphous silica; no dermal data were identified for silica.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the

Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Throughout this toxicological profile, the term *c-silica* refers to crystalline silica; non-crystalline amorphous silica is referred to as *a-silica*. For occupational exposure studies on c-silica compounds, the source of c-silica (e.g., mining, manufacturing) is noted. For studies on a-silica, the specific type of compound (natural or synthetic, type of synthetic, commercial product name) is noted.

Selection of Literature. The literature on the health effects of occupational exposure of humans to inhaled respirable c-silica is extensive, including numerous recently published reviews. This profile describes results of a subset of these studies that provide information on exposure-response relationships. There is also extensive literature on the effects of inhaled c-silica in laboratory animals; however, due to the abundance of information on the effects of c-silica in humans, animal studies on c-silica are not included in this profile. In contrast to the large amount of information available on the effects of inhaled c-silica, much less information is available on the effects of oral exposure to c-silica and inhalation and oral exposure to a-silica; therefore, studies in laboratory animals are reviewed and included in these sections to supplement human data. Studies on adverse effects of dermal exposure to c-silica and a-silica in humans or laboratory animals were not identified in the published literature. Studies included in Chapter 2 were identified primarily from recent reviews, literature searches, and tree-searching of important literature. In addition, results of numerous unpublished oral exposure studies in animals on synthetic a-silica are reported by OECD (2016) and ECHA (2019). Information reviewed in these reports on synthetic a-silica is consistent with published oral exposure. General descriptions of health effects of c-silica and a-silica were taken from numerous, recent reviews, as indicated throughout Chapter 2.

Routes of Exposure. The exposure route of concern for c-silica and a-silica compounds is inhalation. Effects of inhaled c-silica and a-silica are strictly associated with occupational exposure to particles that are of respirable size (<10 µm). Adverse effects of inhaled silica are not observed from incidental exposure to low levels of 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). While synthetic a-silica compounds have initial particle sizes in the nanoparticle range, these particles covalently bond during the manufacturing process to form indivisible aggregates in the respirable range, which can further combine to form micron-sized agglomerates (Fruijtier-Polloth 2012, 2016; Taeger et al. 2016); see Chapter 4 (Chemical and Physical Information) for more details. Due to irreversible formation of aggregates in the respirable range, commercial a-silica products are included in this profile. Nearly all available animal inhalation a-silica studies evaluated synthetic products, and are clearly identified as pyrogenic, precipitated, gel, or colloidal in the subsequent sections of Chapter 2 as well as Table 2-1. If studies did not report particle size mean or distribution or did not indicate that particles were of respirable size, particle size was assumed to be in the respirable range; this is noted in discussion of individual studies.

Oral exposure to c-silica and a-silica does not appear to be an exposure route of concern. Although few studies on oral exposure to c-silica were identified, available studies in laboratory animals, as reviewed in subsequent sections of 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. 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 OECD (2016) and 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 studies evaluating oral exposure to natural a-silica in laboratory animals were identified.

Dermal exposure to c-silica and a-silica also does not appear to be an exposure route of concern. 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 OECD (2016) or ECHA (2019).

Duration of Exposure and Exposure Metric. Adverse effects of c-silica most commonly occur after chronic exposure durations (e.g., several years). Although repeated, high exposures for intermediate exposure durations can produce adverse effects, this is not common. Therefore, an exposure metric that incorporates both concentration of silica in air and exposure duration provides the most comprehensive assessment of exposure. To quantify exposure, key epidemiological studies reviewed in this profile use cumulative exposure, expressed in terms of mg/m^3-year.

Assessment of Exposure. Epidemiology studies of occupational exposures to c-silica have relied on estimates of long-term average or cumulative exposures for exploring associations between exposures and health outcomes. These estimates are reconstructions of actual exposures that occurred to individual subjects. This approach to exposure estimation is used in the absence of direct measurements of long-term exposures (e.g., personal monitoring). A typical exposure reconstruction relies on creation of a job-exposure matrix. Individual subjects are assigned exposures, based on records of their work histories that provide information on the duration of jobs that they performed at a given location. Each job is assigned an exposure level based on reported air monitoring data. Typically, this is based on records of concentrations of respirable particles in work place air. Particle concentrations are converted to approximate equivalent concentrations of c-silica using estimates of the percent c-silica in respirable dust, which is not routinely measured in workplace monitoring programs. Cumulative exposure is estimated from estimates of the average time spent in each job per shift and average number of shifts per year. Exposure estimation introduces uncertainties and potential errors into exposure-response models. Exposure misclassification can result from several sources, such as errors or ambiguities about individual work histories; averaging of measured air concentrations, which may obscure exposure dynamics (e.g., periods of intense exposure); extrapolation of air monitoring data to longer-term averages; or extrapolation of estimates of the average c-silica fraction of respirable particles to specific job categories, individuals, or cohorts. If exposure misclassification occurs at similar rates among outcome cases and non-cases (e.g., nondifferential misclassification), it is likely to bias estimated exposure-response relationships toward the null. Differential misclassification (e.g., misclassification occurs at different rates among cases and non-cases) can result in bias towards the null if cases are mis-assigned to lower exposures, or away from the null if cases are mis-assigned to higher exposures.

Assessment of Health Outcomes. Epidemiology studies of occupational exposures to c-silica have relied on outcome measures obtained from medical records (including death certificates) or functional evaluations (e.g., lung function tests). Use of historical medical records introduces uncertainties and potential errors into exposure-response models. Outcome misclassification can result from errors or ambiguities in the medical records such as recording errors, misdiagnoses, or diagnostic suspicion bias (e.g., medical testing and/or diagnoses are influenced by information about potential exposures). If outcome misclassification occurs at similar rates among exposure categories (e.g., nondifferential misclassification), it is likely to bias estimated exposure-response relationships toward the null. Differential misclassification (e.g., misclassification occurs at different rates among exposure categories) can result in bias towards the null if cases are mis-assigned to lower exposures, or away from the null if cases are mis-assigned to higher exposures. Nondifferential misclassification of outcomes is a potential source of bias when exposure to c-silica is considered in decisions about medical surveillance, testing, or diagnosis.

Confounding Bias. Occupational cohorts studied in c-silica epidemiological studies also experience exposures to other substances and stressors. Confounding bias can occur if these factors are associated with exposure and the outcome but are not causal for the outcome. Typical adjustments used in silica studies include age, sex, and race. However, other potential confounders of importance include exposure to other substances that can cause pneumoconiosis, including asbestos, beryllium, and coal dust. Potential confounders in studies of lung cancer include smoking and exposure to other occupational carcinogens such as arsenic, cadmium, diesel, radon, and talc.

Silica Polymorphs, Surface Structure, and Biological Activity. c-Silica and a-silica exist in several forms (polymorphs), each with different surface chemistry characteristics, including incorporation of trace metals or other compounds (see Section 4.2, Chemical and Physical Properties). The biological activity (e.g., the potential to induce adverse effects) is likely related to surface characteristics (see Section 2.20.2, Mechanisms of Toxicity). Furthermore, for the same polymorph, biological activity may vary due to modifications of surface characteristics from processing or aging. Due to several factors, exposure-response relationships estimated for different silica industries and even within the same silica industry have varied, making it difficult to define exposure-response relationships that apply to general c-silica or a-silica categories. These factors include the form of c-silica contributing to exposure, error in estimation of actual exposures, length of follow-up period, inclusion of decedents, adjustments for smoking status, and other potential confounders.

Overview of Health Effects of Inhaled Silica. The adverse effects of silica are limited to inhalation exposures in occupational settings. No known adverse effects occur from exposure to particles that exceed the respirable size range or from incidental exposure at ambient levels of c-silica or a-silica in the environment (e.g., at beaches).

Health effects of inhaled c-silica. Occupational exposure studies of humans exposed to inhaled respirable c-silica identify adverse effects to the respiratory, renal, and immune systems. In addition, some studies show an association between c-silica exposure and lung cancer. Of these effects, the most sensitive effect of inhaled c-silica is on the respiratory system, specifically silicosis. Renal and immune effects have not been as extensively studied as silicosis and lung cancer, although available evidence supports an association between occupational exposure to c-silica and increased risks for these effects. However, associations between inhaled c-silica and renal and immune effects have not been observed in all studies. Discussions of health effects of inhaled c-silica in Chapter 2 focus only on these main adverse effects of c-silica and do not review other systems. As noted above, animal studies for c-silica were not considered due to the extensive literature on c-silica toxicity in humans.

- **Respiratory Effects.** Respiratory effects of inhaled c-silica are silicosis, mortality due to silicosis, decreased lung function in the absence of silicosis, and COPD. Silicosis, a progressive fibrotic, potentially fatal lung disease caused by occupational exposure to respirable c-silica, is a well-established effect that has been recognized since ancient times. Silicosis does not result from inhalation of any other substance, including a-silica, and is not associated with incidental exposure to low levels of c-silica in the environment (e.g., at beaches). Silicosis is strictly an occupational disease.

- **Renal Effects.** A wide-spectrum of renal pathologies (called silicon nephropathy) has 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., ANCA-associated vasculitis). Relative to silicosis, the incidence of renal disease is very low.

- **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.

- **Lung Cancer.** Numerous occupational exposure studies have found associations between occupational exposure to respirable c-silica and increased risk of lung cancer, although not all studies have found associations.

The Department of Health and Human Services classified c-silica (respirable size) as a Group 1 (definite) human lung carcinogen (NTP 2014). IARC (2012) and NIOSH (2002) also have concluded that c-silica (respirable size) is a human carcinogen.

Health effects of inhaled a-silica. Relative to the large number of occupational studies on c-silica, fewer studies have evaluated the effects of inhaled a-silica in humans. Pulmonary fibrosis has been reported in a-silica workers, although co-exposure to c-silica could not be ruled out. Animal studies show that inhalation of a-silica produces pulmonary inflammation, and reversible fibrosis, but silicosis is not observed. Other than pulmonary effects, no other effects associated with inhaled a-silica have been established.

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
1	Rat (Wistar) 10 M	5 days 6 hours/day (N)	0, 1, 5, 25	BI, BW, CS, FI, HP, OW	Bd Wt Resp	25 M 1 M	5 M		Accumulation of alveolar macrophages, intra-alveolar granulocytic infiltrates, mild bronchial/bronchiolar hypertrophy
Synthetic a-silica: Pyrogenic silica (Cab-O-Sil M5) Arts et al. 2007									
2	Rat (Wistar) 10 M,10 F	5 days 6 hours/day (N)	0, 1, 5, 25	BI, BW, CS, FI, HP, OW	Bd Wt Resp	25 1	5		Intra-alveolar granulocytic infiltrates, mild bronchial/bronchiolar hypertrophy
Synthetic a-silica: Precipitated silica (Zeosil 45) Arts et al. 2007									
3	Rat (Wistar) 10 M	5 days 6 hours/day (N)	0, 1, 5, 25	BI, BW, CS, FI, HP, OW	Bd Wt Resp	25 M 5 M	25 M		Accumulation of alveolar macrophages, mild bronchial/bronchiolar hypertrophy
Synthetic a-silica: Silica gel (Syloid 74) Arts et al. 2007									
4	Rat (Wistar) 10 M,10 F	2 weeks 5 days/week 6 hours/day (WB)	0, 17, 44, 164	BW, CS, FI, HE, OW, GN, HP	Resp			17	Respiratory distress, inflammation, pneumonia, granulomas
Synthetic a-silica: Pyrogenic hydrophilic silica (Aerosil 200) Reuzel et al. 1991									
5	Rat (Wistar) 10 M,10 F	2 weeks 5 days/week 6 hours/day (WB)	0, 46, 170, 680	BW, CS, FI, HE, OW, GN, HP	Resp			46	Respiratory distress, increased lung weight, increased cellularity, pneumonia
Synthetic a-silica: Precipitated hydrophobic (Sipernat 22S) Reuzel et al. 1991									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
6	Rat (Wistar) 10 M,10 F	2 weeks 5 days/week 6 hours/day (WB)	0, 31, 87, 209	BW, CS, FI, HE, OW, GN, HP	Death			209	4/10 M died, 2/10 F died
					Resp			31	Increased lung weight, respiratory distress, increased cellularity, edema, granulomas
Synthetic a-silica: Pyrogenic hydrophobic silica (Aerosil R 974) Reuzel et al. 1991									
7	Rat (Crl:CD BR) 6 M	2 weeks 5 days/week 6 hours/day (N)	0, 10.1, 50.5, 154	BI	Resp	10.1 M	50.5 M		25-fold increase of neutrophils in BAL
Synthetic a-silica: Colloidal silica (Ludox) Warheit et al. 1991, 1995									
8	Rat (Crl:CD BR) 24 M	3 days 6 hours/day (N)	0, 10, 100	BI	Resp		10 M		40% increased neutrophils and 200% increased LDH activity in BAL
Synthetic a-silica: Precipitated silica (Zeofree 80) Warheit et al. 1995									
9	Guinea pig (albino) 9 B	8 hours (WB)	0, 53	GN, HP	Resp		53		Macrophage infiltration, dilatation of bronchioles and alveolar ducts
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957b									
10	Guinea pig (albino) 4 B	24 hours (WB)	0, 53	GN, HP	Resp		53		Macrophage infiltration, alveolar hyperemia, focal petechiae, moderate bronchiole epithelial desquamation, slight apical emphysema
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957b									
INTERMEDIATE EXPOSURE									
11	Rat (Fischer-344) 4 M	13 weeks 5 days/week 6 hours/day (WB)	0, 50.4	BI, HP	Resp			50.4 M	Lung inflammation, proliferative responses, fibrosis
Synthetic a-silica: Pyrogenic hydrophilic silica (Aerosil 200) Johnston et al. 2000									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
12	Rat (Crl:DC BR) 25 M	4 weeks 5 days/week 6 hours/day	0, 10, 50, 150	BC, BW, CS, HE, HP, OW, UR	Bd Wt	150 M			
					Resp	10 M	50 M		Inflammation, hyperplasia
					Hepatic	150 M			
					Renal	150 M			
Synthetic a-silica: Colloidal silica (Ludox) Lee and Kelly 1992									
13	Rat (Wistar) 70 M,70 F	13 weeks 5 days/week 6 hours/day (WB)	0, 1, 6, 30	BC, BI, BW, CS, FI, HE, OW, GN, HP, UR	Bd Wt	30			
					Resp			1	Increased cellularity, inflammation, increased collagen content, fibrosis
					Cardio	30			
					Gastro	30			
					Hemato	6	30		2–3-fold increase in neutrophils
					Musc/skel	30			
					Hepatic	30			
					Renal	30			
					Dermal	30			
					Ocular	30			
					Endocr	30			
					Immuno	30			
					Neuro	30			
					Repro	30			
Synthetic a-silica: Pyrogenic hydrophilic silica (Aerosil 200) Reuzel et al. 1991									
14	Rat (Wistar) 70 M,70 F	13 weeks 5 days/week 6 hours/day (WB)	0, 30	BC, BI, BW, CS, FI, HE, OW, GN, HP, UR	Bd Wt	30			
					Resp			30	Increased lung weight, increased cellularity, inflammation, granuloma, increased collagen content
					Cardio	30			
					Gastro	30			
					Musc/skel	30			
					Hepatic	30			

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Renal	30			
					Dermal	30			
					Ocular	30			
					Endocr	30			
					Immuno	30			
					Neuro	30			
					Repro	30			
Synthetic a-silica: Pyrogenic hydrophobic silica (Aerosil R 974) Reuzel et al. 1991									
15	Rat (Wistar) 70 M,70 F	13 weeks 5 days/week 6 hours/day (WB)	0, 30	BC, BI, BW, CS, FI, HE, OW, FN, HP, UR	Bd Wt	30			
					Resp			30	Increased lung weight, increased cellularity, inflammation, increased collagen content
					Cardio	30			
					Gastro	30			
					Hemato	30			
					Musc/skel	30			
					Hepatic	30			
					Renal	30			
					Dermal	30			
					Ocular	30			
					Endocr	30			
					Immuno	30			
					Neuro	30			
					Repro	30			
Synthetic a-silica: Precipitated hydrophobic (Sipernat 22S) Reuzel et al. 1991									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
16	Rat (Wistar) 5 M	4–6 months 5 days/week 7 hours/day (WB)	0, 10.9	HP, OW	Resp		10.9 M		Macrophage infiltration in lung-associated lymph nodes; enlarged pulmonary lymph nodes
Synthetic a-silica: Vitreous a-silica (NS) Rosenbrunch 1992									
17	Rat (S-D) 35–42 B	3–12 months 5 days/week 8 hours/day (WB)	0, 53	LE, GN, HP	Death			53	96% mortality; majority of deaths occurred between 4 and 9 months
					Resp		53		Macrophage infiltration, cellular nodules, focal emphysema
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957a [classified at intermediate because only one animal survived until 12-month terminal sacrifice]									
18	Rat (Crl:CD BR) 6 M	4 weeks 5 days/week 6 hours/day (N)	0, 10.1, 50.5, 154	BI	Resp	10.1 M	50.5 M		200-fold increase of neutrophils in BAL
Synthetic a-silica: Colloidal silica (Ludox) Warheit et al. 1991, 1995									
19	Guinea pig (albino) 42 B	2–10 months 5 days/week 8 hours/day (WB)	0, 53	LE, GN, HP	Resp			53	Macrophage infiltration, alveolar vacuolation, stenosis, focal fibrosis, emphysema
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957b									
20	Rabbit (New Zealand) 6 M, 4 F	3–12 months 5 days/week 8 hours/day (WB)	0, 53	LE, CS, BW, GN, HE, HP, OF	Resp			53	Macrophage infiltration, cellular nodules, ductal stenosis, emphysema, collagen deposition
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957c [Study classified as intermediate because only 1 rabbit survived until 12-month sacrifice; most died due to experimental error]									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
21	Rabbit (NS) 39 NS	50 weeks 5 days/week 8 hours/day (WB)	0, 72 (TWA)	LE, BW, GN, HP	Death			124	18/39 died
					Resp		72		Macrophage infiltration, alveolar epithelization
Natural a-silica: Raw diatomaceous earth (0% c-silica) Tebbens et al. 1957									
CHRONIC EXPOSURE									
22	Monkey (Cynomolgus) 7–10 M	13 months 5 days/week 6 hours/day (WB)	0, 9.4	BC, BW, CS, FI, HE, HP, OW, OF	Bd Wt	9.4 M			
					Resp		9.4 M		Macrophage/mononuclear cell aggregates, impaired pulmonary function
					Cardio	9.4 M			
					Gastro	9.4 M			
					Hemato	9.4 M			
					Hepatic	9.4 M			
					Renal	9.4 M			
					Dermal	9.4 M			
					Endocr	9.4 M			
					Immuno	9.4 M			
					Repro	9.4 M			
Synthetic a-silica: Silica gel (NS) Groth et al. 1981									
23	Monkey (Cynomolgus) 9–10 M	13 months 5 days/week 6 hours/day (WB)	0, 9.9	BC, BW, CS, FI, HE, HP, OW, OF	Bd Wt	9.9 M			
					Resp		9.9 M		Macrophage/mononuclear cell aggregates, impaired pulmonary function
					Cardio	9.9 M			
					Gastro	9.9 M			
					Hemato	9.9 M			
					Hepatic	9.9 M			
					Renal	9.9 M			
					Dermal	9.9 M			
					Endocr	9.9 M			
					Immuno	9.9 M			

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Repro	9.9 M			
Synthetic a-silica: Pyrogenic silica (NS) Groth et al. 1981									
24	Monkey (Cynomolgus) 10 M	18 months 5 days/week 6 hours/day (WB)	0, 6.9	BC, BW, CS, FI, HE, HP, OW, OF	Bd Wt	6.9 M			
					Resp		6.9 M		Macrophage/mononuclear cell aggregates, impaired pulmonary function
					Cardio	6.9 M			
					Gastro	6.9 M			
					Hemato	6.9 M			
					Hepatic	6.9 M			
					Renal	6.9 M			
					Dermal	6.9 M			
					Endocr	6.9 M			
					Immuno	6.9 M			
					Repro	6.9 M			
Synthetic a-silica: Precipitated silica (NS) Groth et al. 1981									
25	Monkey (Macaque) 5–15F	12 months 8 hours/day 5 days/week (WB)	0, 15	BW, CS, GN, HP	Resp		15 F		Macrophage infiltration, emphysema, bronchiole and alveolar hypertrophy, stenosis, fibrosis and slight collagen deposition
					Cardio		15 F		Cardiac hypertrophy
					Hepatic		15 F		Hepatocellular vacuolization
					Renal		15 F		Renal congestion and cloudy swelling of the convoluted tubules
					Endocr	15 F			
					Immuno	15 F			
Synthetic a-silica: Precipitated silica (NS) Schepers 1962									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
26	Rat (Sprague-Dawley) 13 M	12 months 5 days/week 6 hours/day (WB)	0, 9.9	BC, BW, CS, FI, HP, HE, OW	Bd Wt	9.9 M			
					Resp	9.9 M			
					Cardio	9.9 M			
					Gastro	9.9 M			
					Hemato	9.9 M			
					Hepatic	9.9 M			
					Renal	9.9 M			
					Dermal	9.9 M			
					Endocr	9.9 M			
					Immuno	9.9 M			
					Repro	9.9 M			
Synthetic a-silica: Pyrogenic silica (NS) Groth et al. 1981									
27	Rat (Sprague-Dawley) 24 M	12 months 5 days/week 6 hours/day (WB)	0, 9.4	BC, BW, CS, FI, HP, HE, OW	Bd Wt	9.4 M			
					Resp	9.4 M			
					Cardio	9.4 M			
					Hemato	9.4 M			
					Hepatic	9.4 M			
					Renal	9.4 M			
					Dermal	9.4 M			
					Endocr	9.4 M			
					Immuno	9.4 M			
					Repro	9.4 M			
Synthetic a-silica: Silica gel (NS) Groth et al. 1981									
28	Rat (Sprague-Dawley) 19 M	12 months 5 days/week 6 hours/day (WB)	0, 6.9	BC, BW, CS, FI, HE, HP, OW	Bd Wt	6.9 M			
					Resp	6.9 M			
					Cardio	6.9 M			
					Gastro	6.9 M			
					Hemato	6.9 M			
					Hepatic	6.9 M			

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Renal	6.9 M			
					Dermal	6.9 M			
					Endocr	6.9 M			
					Immuno	6.9 M			
					Repro	6.9 M			
Synthetic a-silica: Precipitated silica (NS) Groth et al. 1981									
29	Rat (Wistar) 10–15 M	12 months 5 days/week 7 hours/day (WB)	0, 10.9	HP, OW	Resp		10.9 M		Macrophage infiltration in lung-associated lymph nodes, enlarged pulmonary lymph nodes
Synthetic a-silica: Vitreous a-silica (NS) Rosenbrunch 1992									
30	Rat (NS) 50–57 NS	15 months 7 days/week 8 hours/day (WB)	0, 126	OW, HP	Resp		126		Increased lung weight, macrophage accumulation
Synthetic a-silica: Precipitated silica (HI-SIL 233) Schepers 1981									
31	Guinea pig (Hartley) 15 M	12 months 5 days/week 6 hours/day (WB)	0, 9.9	BC, BW, CS, FI, HE, HP, OW	Bd Wt	9.9 M			
					Resp	9.9 M			
					Cardio	9.9 M			
					Gastro	9.9 M			
					Hemato	9.9 M			
					Hepatic	9.9 M			
					Renal	9.9 M			
					Dermal	9.9 M			
					Endocr	9.9 M			
					Immuno	9.9 M			
					Repro	9.9 M			
Synthetic a-silica: Pyrogenic silica (NS) Groth et al. 1981									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
32	Guinea pig (Hartley) 15 M	12 months 5 days/week 6 hours/day (WB)	0, 6.9	BC, BW, CS, FI, HE, HP, OW	Bd Wt	6.9 M			
					Resp	6.9 M			
					Cardio	6.9 M			
					Gastro	6.9 M			
					Hemato	6.9 M			
					Hepatic	6.9 M			
					Renal	6.9 M			
					Dermal	6.9 M			
					Endocr	6.9 M			
					Immuno	6.9 M			
					Repro	6.9 M			
Synthetic a-silica: Precipitated silica (NS) Groth et al. 1981									
33	Guinea pig (Hartley) 15 M	12 months 5 days/week 6 hours/day (WB)	0, 9.4	BC, BW, CS, FI, HE, HP, OW	Bd Wt	9.4 M			
					Resp	9.4 M			
					Cardio	9.4 M			
					Gastro	9.4 M			
					Hemato	9.4 M			
					Hepatic	9.4 M			
					Renal	9.4 M			
					Dermal	9.4 M			
					Endocr	9.4 M			
					Immuno	9.4 M			
					Repro	9.4 M			
Synthetic a-silica: Silica gel (NS) Groth et al. 1981									

Table 2-1. Levels of Significant Exposure to Silica – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
34	Guinea pig (NS) 82–100 NS	24 months 7 days/week 8 hours/day (WB)	0, 126	OW, HP	Resp		126		Increased lung weight, macrophage accumulation
Synthetic a-silica: Precipitated silica (HI-SIL 233) Schepers 1981									
35	Guinea pig (albino) 42 B	12–24 months 5 days/week 8 hours/day (WB)	0, 53	LE, GN, HP	Resp			53	Macrophage infiltration, alveolar vacuolation, stenosis, fibrosis, emphysema
Synthetic a-silica: Pyrogenic silica (NS) Schepers et al. 1957b									
36	Rabbit (New Zealand) NS	up to 24 months 5 days/week 8 hours/day (WB)	0, 30, 130, 260	LE, CS, BW, BC, HE, OF	Death			130	>50% mortality
					Resp			30	Dyspnea, macrophage infiltration, stenosis, emphysema, sclerosis and epithelization, granulomatosis
					Cardio		30		Hypertension, ventricular and auricular hypertrophy
Synthetic a-silica (NS) Schepers 1959									
37	Rabbit (NS) 10 exposed, 50 control (NS)	12 months 7 days/week 8 hours/day (WB)	0, 126	OW, HP, OF, HE	Resp		126		Macrophage accumulation
					Cardio		126		Increased cardiac ventricular pressure
Synthetic a-silica: Precipitated silica (HI-SIL 233) Schepers 1981									

[a]The number corresponds to entries in Figure 2-1; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-1. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

a-silica = amorphous silica; B = both male(s) and female(s); BAL = bronchoalveolar lavage; BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; c-silica = crystalline silica; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; (N) = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis; (WB) = whole body

Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Acute (≤14 days)

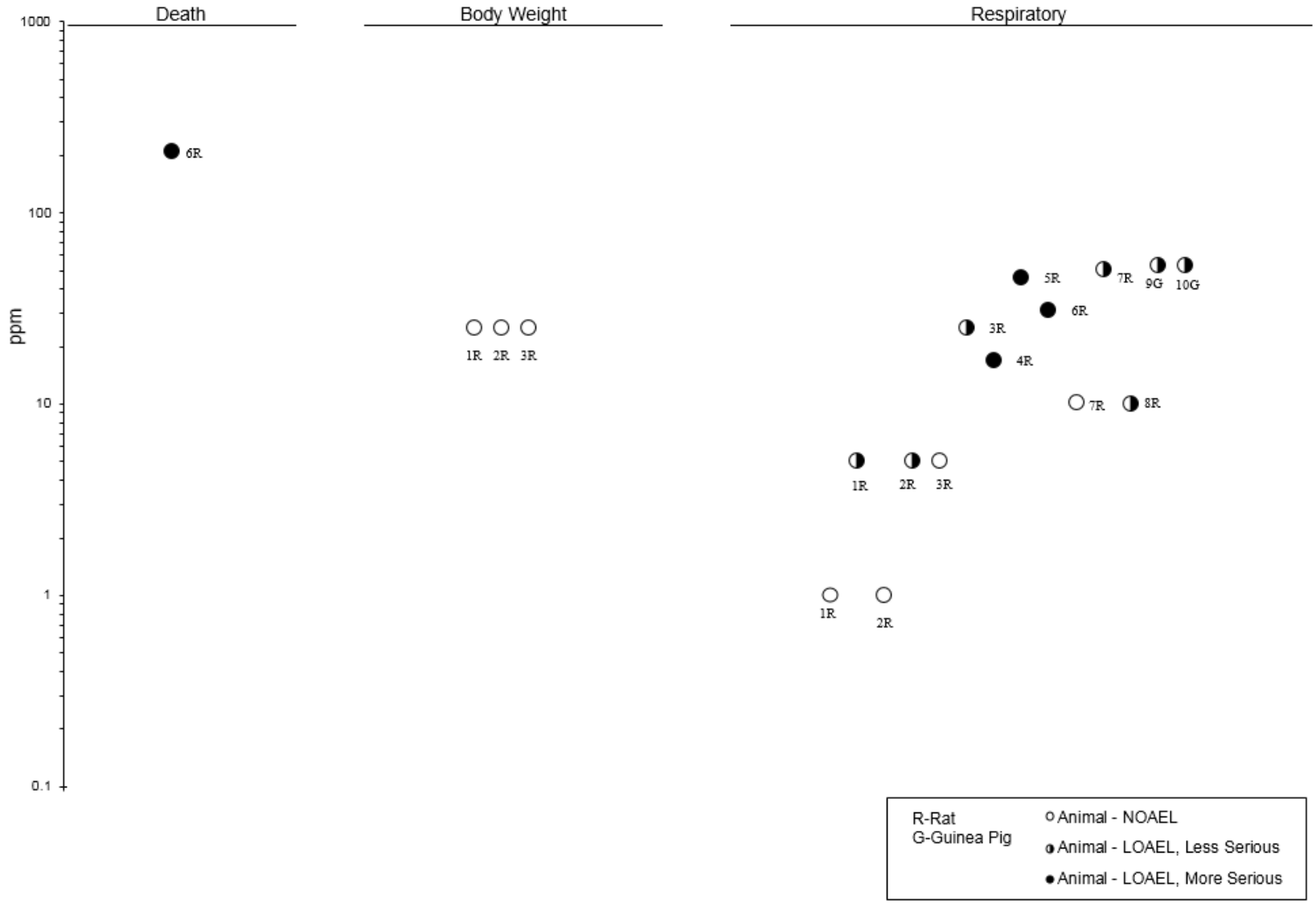


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Intermediate (15-364 days)

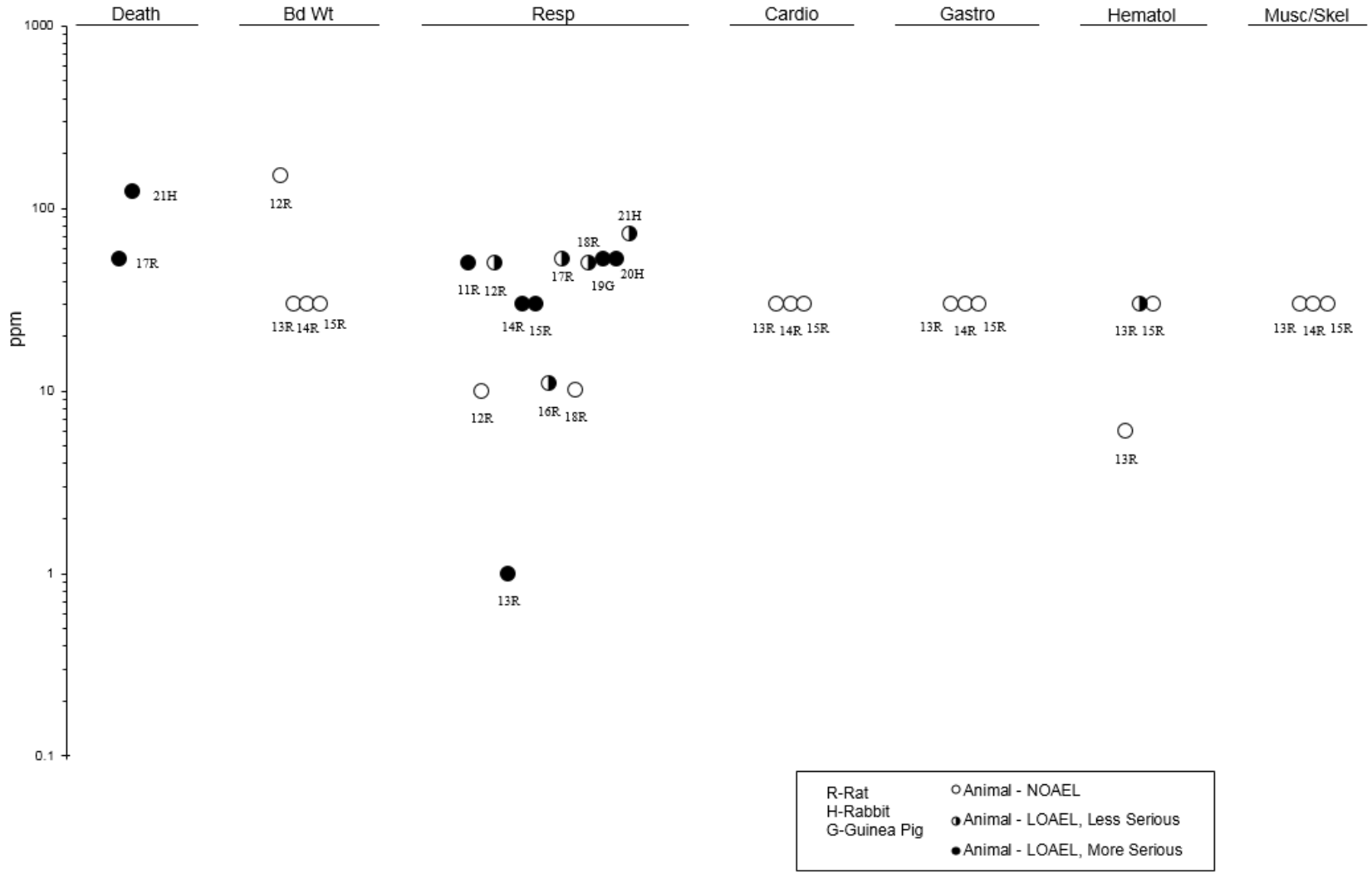


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Intermediate (15-364 days)

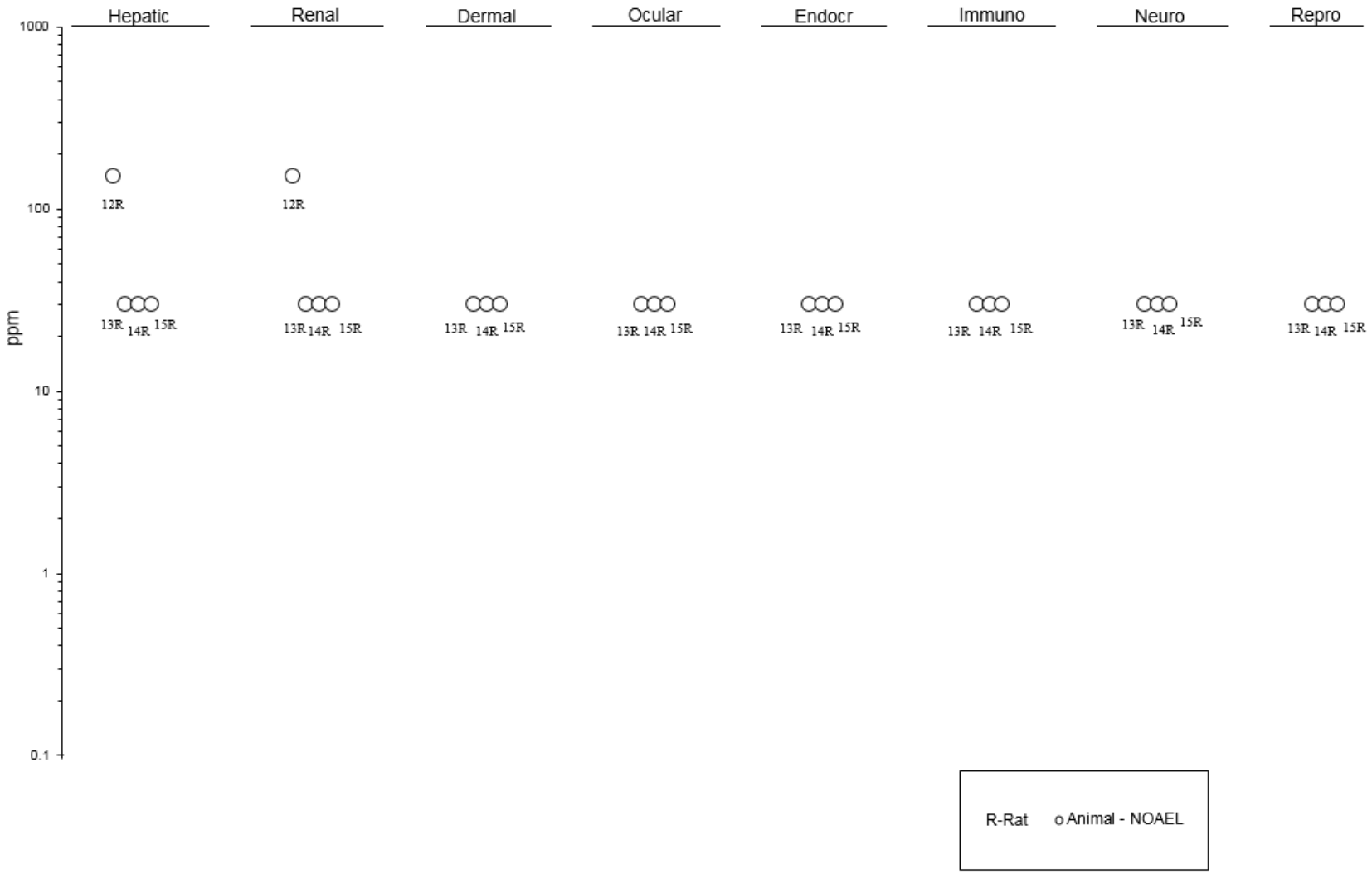


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

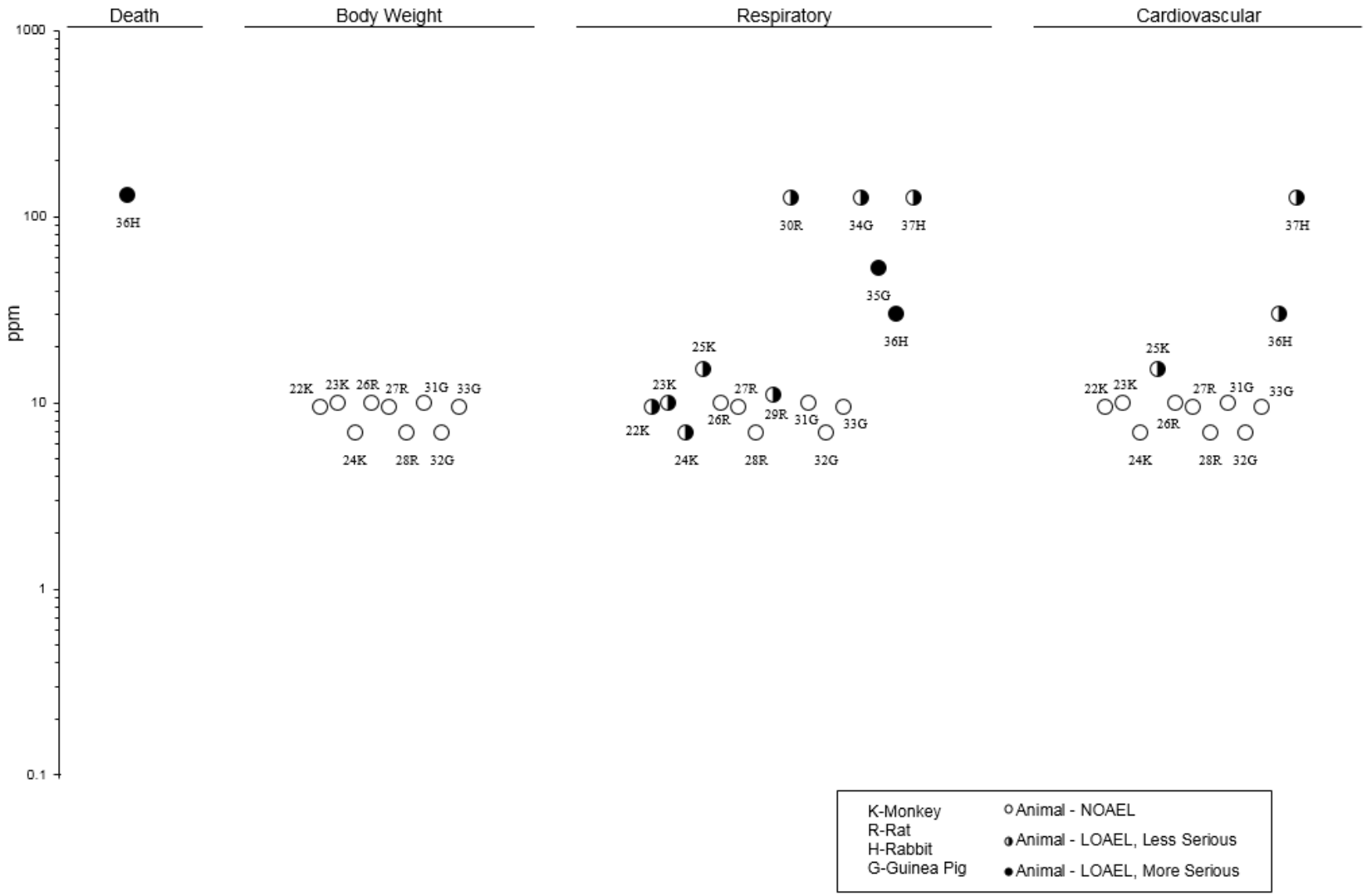


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

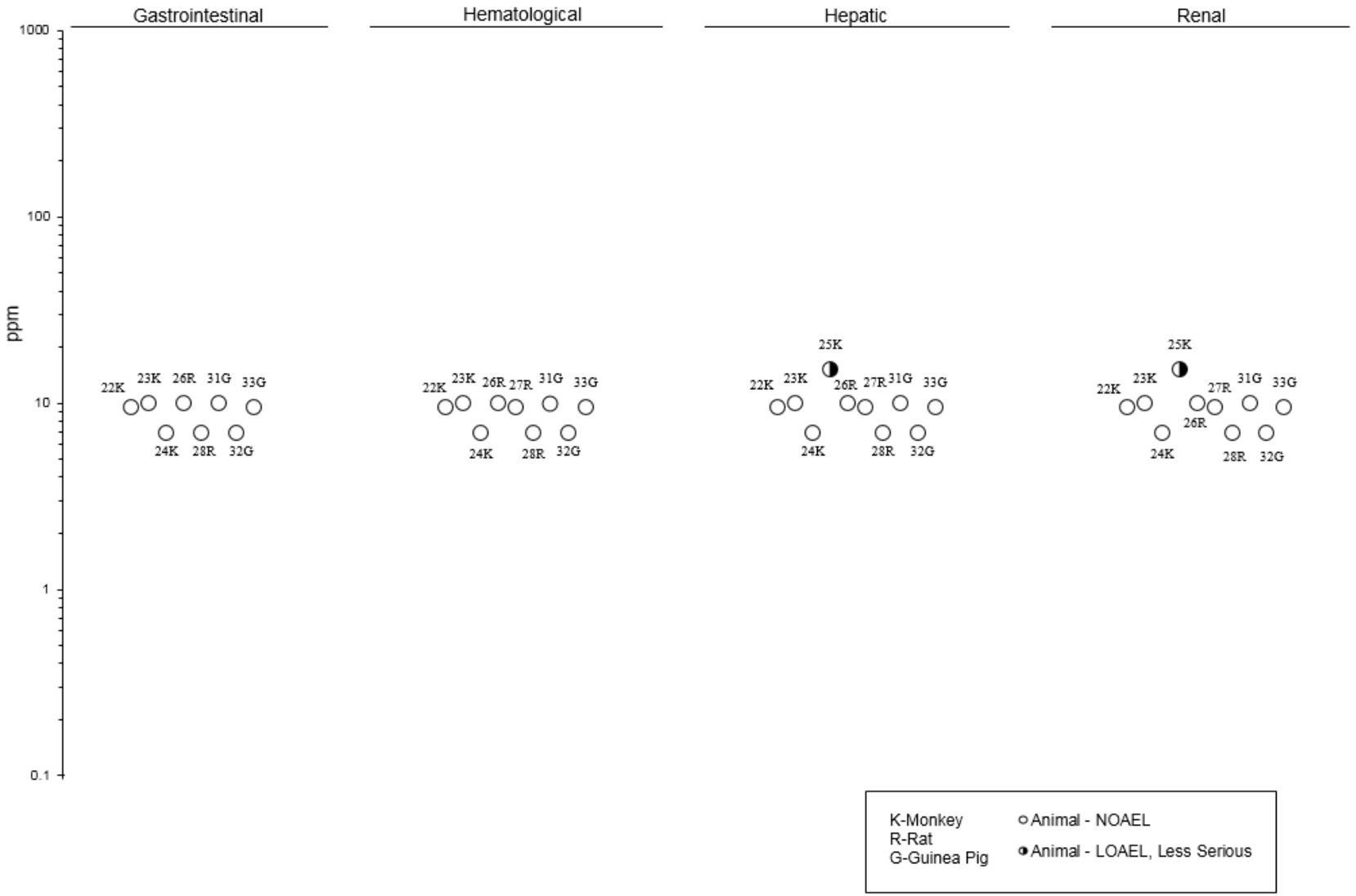


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

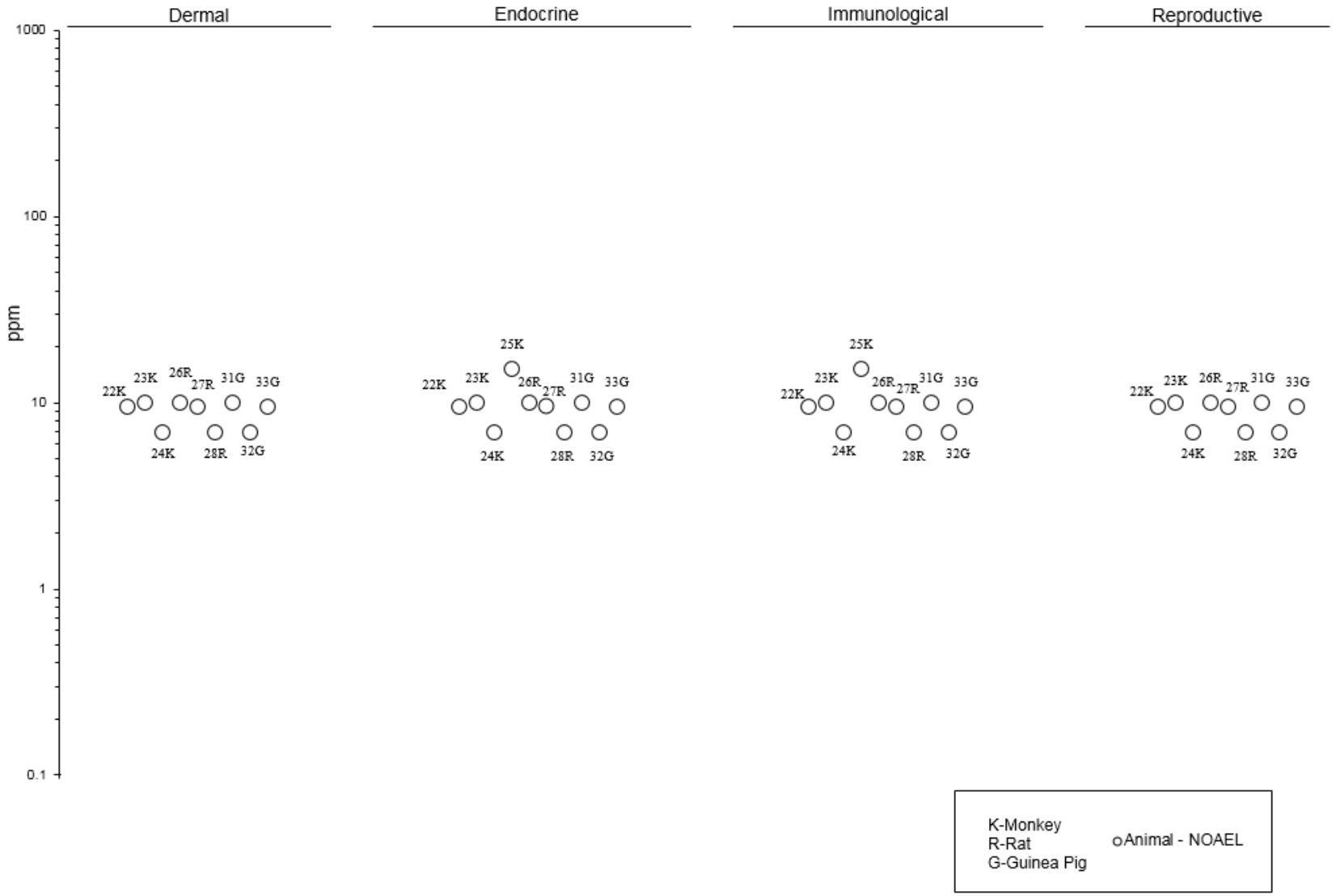


Table 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (albino) 10 M	8 days (W)	0, 50	BW, FI, WI, OF, UR	Bd Wt Renal	50 M 50 M			
Sodium metasilicate **Oner et al. 2005, 2006**									
INTERMEDIATE EXPOSURE									
2	Guinea pig (NS) 6 M	4 months 5 days/week (W)	0.04, 51	HP	Renal	51 M			
Granite **Dobbie and Smith 1982**									
3	Guinea pig (NS) 6 M	4 months 5 days/week (W)	0.04, 51	HP	Renal	51 M			
Quartz **Dobbie and Smith 1982**									
CHRONIC EXPOSURE									
4	Human 7,598 F	NS (W)	0.13	BH, OF	Neuro	0.13 F			Cognitive function did not decline with increasing silica content in drinking water.
Unspecified **Gillette-Guyonnet et al. 2005**									
5	Human 3,777 B	NS (W)	0.15	BH, OF	Neuro	0.15			Cognitive function did not decline with increasing silica content in drinking water.
Unspecified **Jacqmin-Gadda et al. 1996**									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

B = both male and female; Bd Wt or BW = body weight; BH = behavior; F = female(s); FI = food intake; HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; UR = urinalysis; (W) = water; WI = water intake

Figure 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Acute (≤14 days)

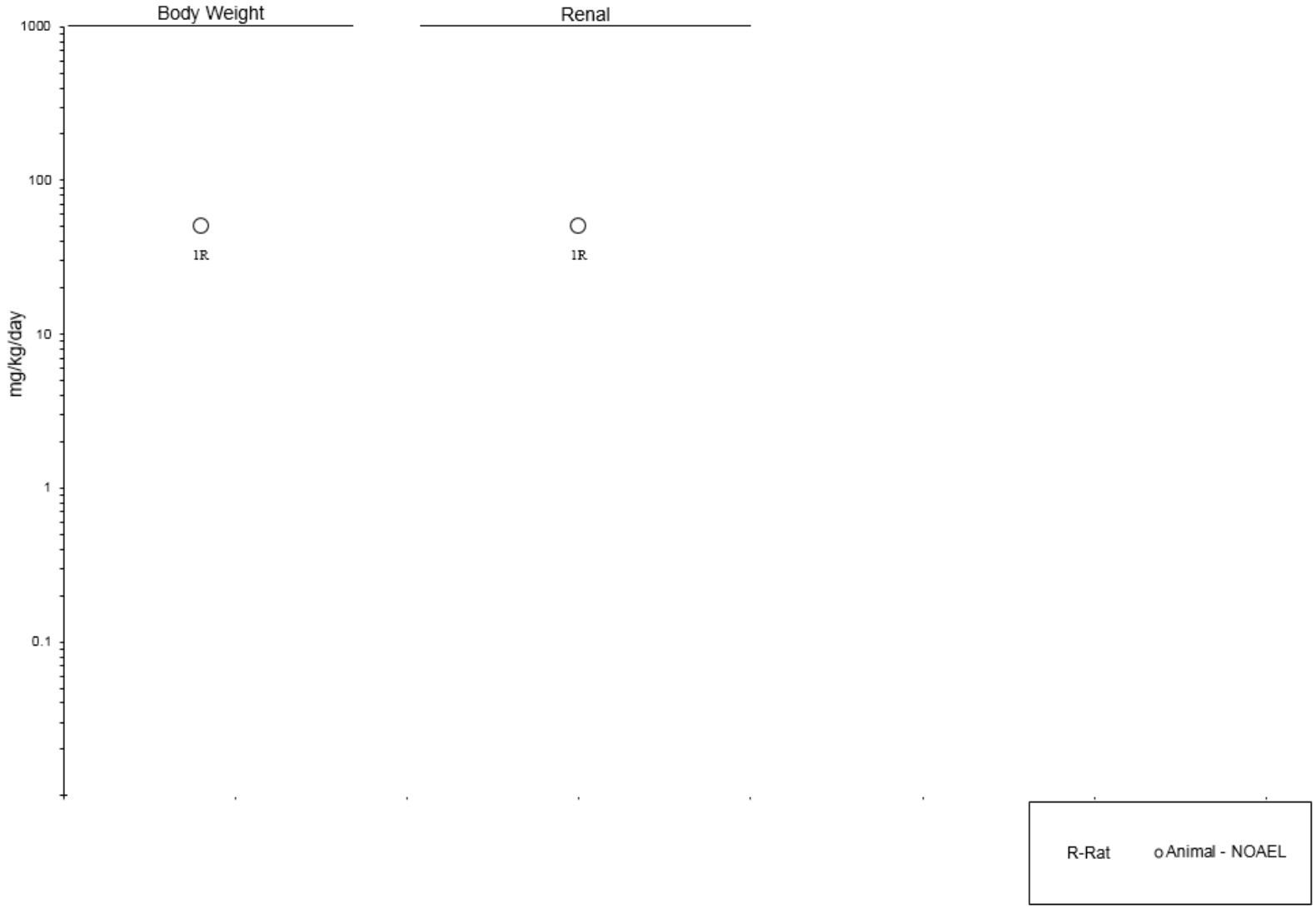


Figure 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Intermediate (15-364 days)

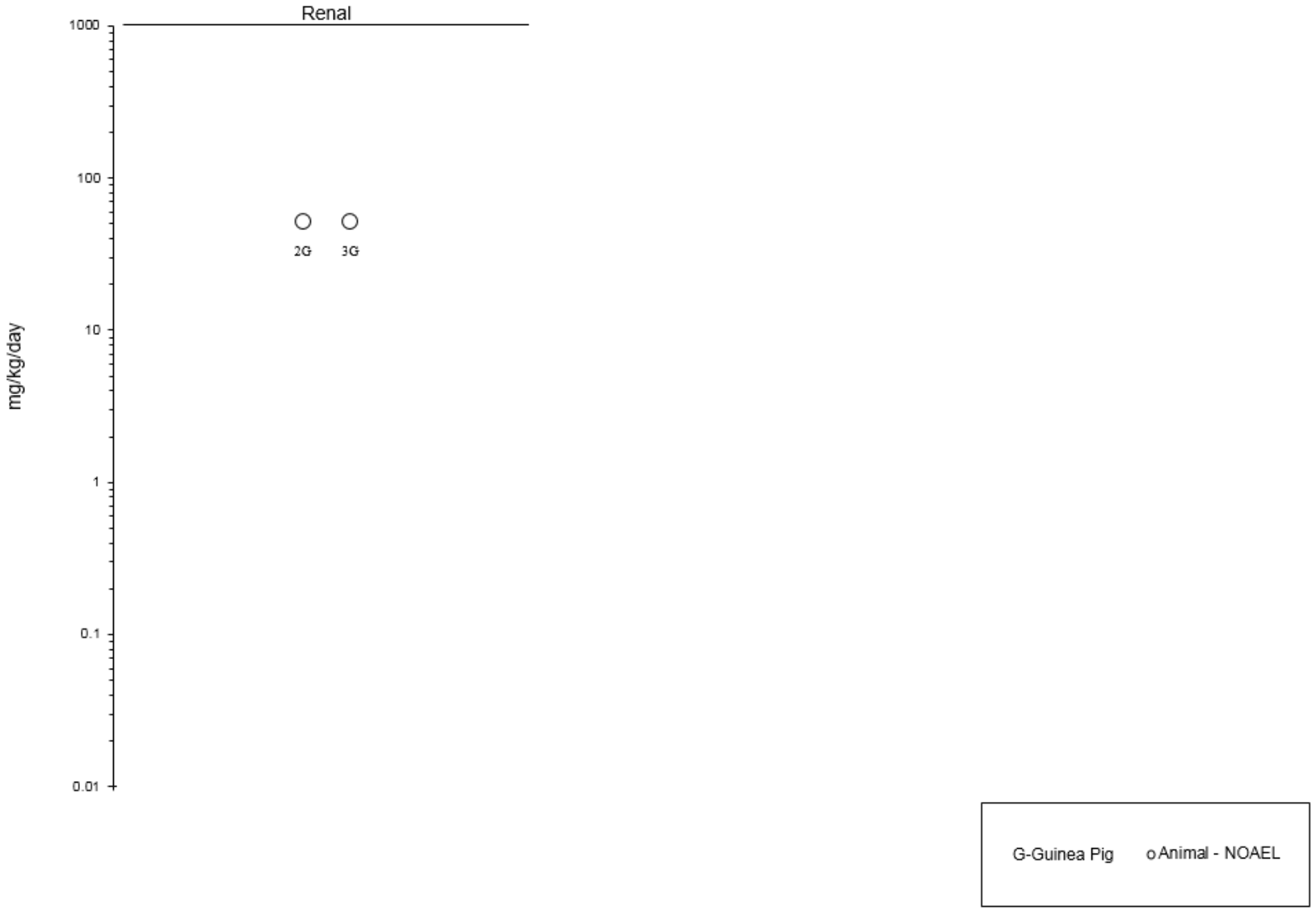


Figure 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Chronic (≥365 days)

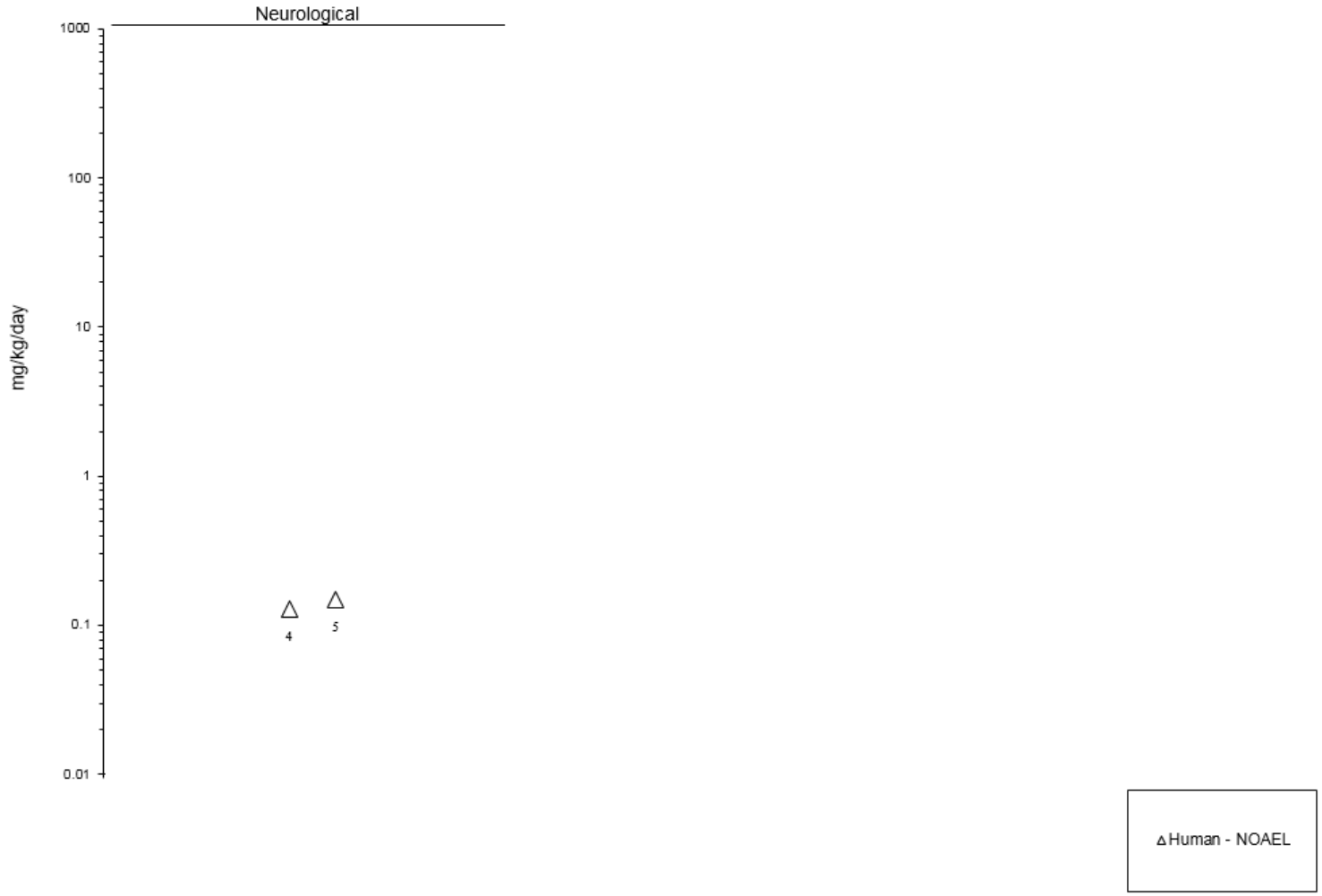


Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 10 M,10 F	Once (GO)	2,500, 5,000 mg/kg	BW, CS, FI, GN, LE	Bd Wt	5,000			
Synthetic a-silica: Pyrogenic silica (Aerosil R 972) **Lewinson et al. 1994**									
2	Rat (Sprague-Dawley) 10 M,10 F	Once (GO)	5,040, 6,350, 7,900	BW, CS, FI, GN, LE	Bd Wt	7,900			
Synthetic a-silica: Precipitated silica (Sipernat D 17) **Lewinson et al. 1994**									
3	Rat (Wistar) 10 M,10 F	2 weeks (F)	2,000, 4,000, 8,000, 16,000	LE	Death			16,000	20% mortality
Synthetic a-silica: Pyrogenic silica (Aerosil R 972) **Lewinson et al. 1994** [The same animals were used in each dose group; dose was increased in step-wise manner every 2 weeks]									
INTERMEDIATE EXPOSURE									
4	Rat (Wistar) 10 M,10 F	5–8 weeks (F)	0, 500, 1,000, 7,500 (TWA)	BW, CS, FI, GN, HE, HP	Bd Wt	1,000	7,500		Decreased body weight
					Hemato	7,500			
					Hepatic	1,000	7,500		Severe atrophy of liver epithelium
					Renal	7,500			
Synthetic a-silica: Pyrogenic silica (Aerosil R 972) **Lewinson et al. 1994** [High-dose group used step-wise increases from 2,000 to 16,000 mg/kg/day, doubling every 2 weeks]									

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
5	Rat (Wistar) 20 M, 20 F	6 months (F)	0, 500	BW, CS, FI, GN, HE, HP, OW	Bd Wt	500			
					Resp	500			
					Cardio	500			
					Gastro	500			
					Hemato	500			
					Hepatic	500			
					Renal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
Synthetic a-silica: Pyrogenic silica (Aerosil R 972) Lewinson et al. 1994									
6	Rat (Wistar) 10 F, 2 M	6 months 1 generation (F)	0, 500	BW, CS, FI, OF, DX	Repro	500			
					Develop	500			
Synthetic a-silica: Pyrogenic silica (Aerosil R 972) Lewinson et al. 1994									
7	Rat (CD) 15 M, 15 F	4 weeks (F)	0, 800	BC, BW, CS, HE, OW, HP, UR	Bd Wt	800			
					Hemato	800			
					Renal	800			
Silicon dioxide (NS) Newberne and Wilson 1970									

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
8	Rat (F344) 10 M,10 F	26 weeks (F)	M: 0, 530, 1,080, 2,220 F: 0, 570, 1,160, 2,410	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	2,410 F 2,220 M			
					Cardio	1,160 F 2,220 M	2,410 F		14% decrease in heart weight
					Hemato	2,410 F 2,220 M			
					Hepatic	2,410 F 2,220 M			
					Renal	2,410 F 2,220 M			
					Immuno	1,160 F 2,220 M	2,410 F		18% decrease in spleen weight
					Neuro	2,410 F 2,220 M			
Synthetic a-silica: Silica gel (Syloid 244) **Takizawa et al. 1988**									
9	Rat (Wistar) 28 M, 28 F	~18 weeks/ generation 2 generations (G)	0, 100, 300, 1,000	BW, FI, CS, DX, GN, HP, OW, OF	Bd Wt	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			
					Neuro	1,000			
					Repro	1,000			
					Develop	1,000			
Synthetic a-silica: Precipitated silica (NM-200) **Woterbeek et al. 2015** [vehicle was MHCP]									

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
10	Mouse (B6C3F1) 10 M,10 F	26 weeks (F)	M: 0, 1,560, 3,280, 6,700 F: 0, 2070, 3,780, 9,810	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	9,810 F 6,700 M			
					Cardio	2,070 F 6,700 M	3,780 F		19% decrease in heart weight
					Hemato	9,810 F 6,700 M			
					Hepatic	3,780 F 6,700 M	9,810 F		16% decrease in liver weight
					Renal	2,070 F 6,700 M	3,780 F		15% decrease in kidney weight
					Immuno	9,810 F 3,280 M	6,700 M		20% decrease in spleen weight
					Neuro	9,810 F 6,700 M			
Synthetic a-silica: Silica gel (Syloid 244) Takizawa et al. 1988									
11	Dog (Beagle) 6–9 M, 6–8 F	4 weeks (F)	0, 800	BC, BW, CS, HE, OW, HP, UR	Bd Wt Hemato Renal	800 800 800			
Silicon dioxide (NS) Newberne and Wilson 1970									
CHRONIC EXPOSURE									
12	Rat (F344) 10 M,10 F	52 weeks (F)	M: 0, 490, 990, 2,030 F: 0, 530, 1,080, 2,220	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	2,220 F 2,030 M			
					Cardio	2,220 F 2,030 M			
					Hemato	2,220 F 2,030 M			
					Hepatic	2,220 F 2,030 M			

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	2,220 F			
						2,030 M			
					Immuno	2,220 F			
						2,030 M			
					Neuro	2,220 F			
						2,030 M			
Synthetic a-silica: Silica gel (Syloid 244) **Takizawa et al. 1988**									
13	Rat (F344) 17–19 M, 17–21 F	103 weeks (F)	M: 0, 450, 910, 1,900 F: 0, 480, 980, 2,020	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	2,020 F			
						1,900 M			
					Cardio	2,020 F			
						1,900 M			
					Hemato	2,020 F			
						1,900 M			
					Hepatic	480 F	980 F		14% decrease in liver weight
						1,900 M			
					Renal	2,020 F			
						1,900 M			
					Immuno	2,020 F			
						1,900 M			
					Neuro	2,020 F			
						1,900 M			
					Cancer				No exposure-related neoplasms
Synthetic a-silica: Silica gel (Syloid 244) **Takizawa et al. 1988**									

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
14	Mouse (B6C3F1) 10 M,10 F	52 weeks (F)	M: 0, 1,410, 2,960, 6,100 F: 0, 1,640, 2,970, 7,560	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	7,560 F 6,100 M			
					Cardio	1,640 F 6,100 M	2,970 F		13% decrease in heart weight
					Hemato	7,560 F 6,100 M			
					Hepatic	7,560 F 6,100 M			
					Renal	7,560 F 6,100 M			
					Immuno	7,560 F 6,100 M			
					Neuro	7,560 F 6,100 M			
Synthetic a-silica: Silica gel (Syloid 244) Takizawa et al. 1988									
15	Mouse (B6C3F1) 18–20 M, 18–20 F	93 weeks (F)	M: 0, 1,310, 2,810, 5,910 F: 0, 1,410, 2,480, 6,010	BC, BW, CS, FI, GN, HE, HP, LE, OW	Bd Wt	6,010 F 5,910 M			
					Cardio	6,010 F 5,910 M			
					Hemato	6,010 F 5,910 M			
					Hepatic	6,010 F 5,910 M			
					Renal	6,010 F 5,910 M			
					Immuno	6,010 F 5,910 M			

Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	6,010 F 5,910 M			
					Cancer				No exposure-related neoplasms
Synthetic a-silica: Silica gel (Syloid 244) **Takizawa et al. 1988**									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

a-silica = amorphous silica; BC = serum (blood) chemistry; Bd Wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F344 = Fischer-344; (F) = food; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MHCP = methylhydroxypropylcellulose; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis

Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Acute (≤14 days)

Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Intermediate (15-364 days)

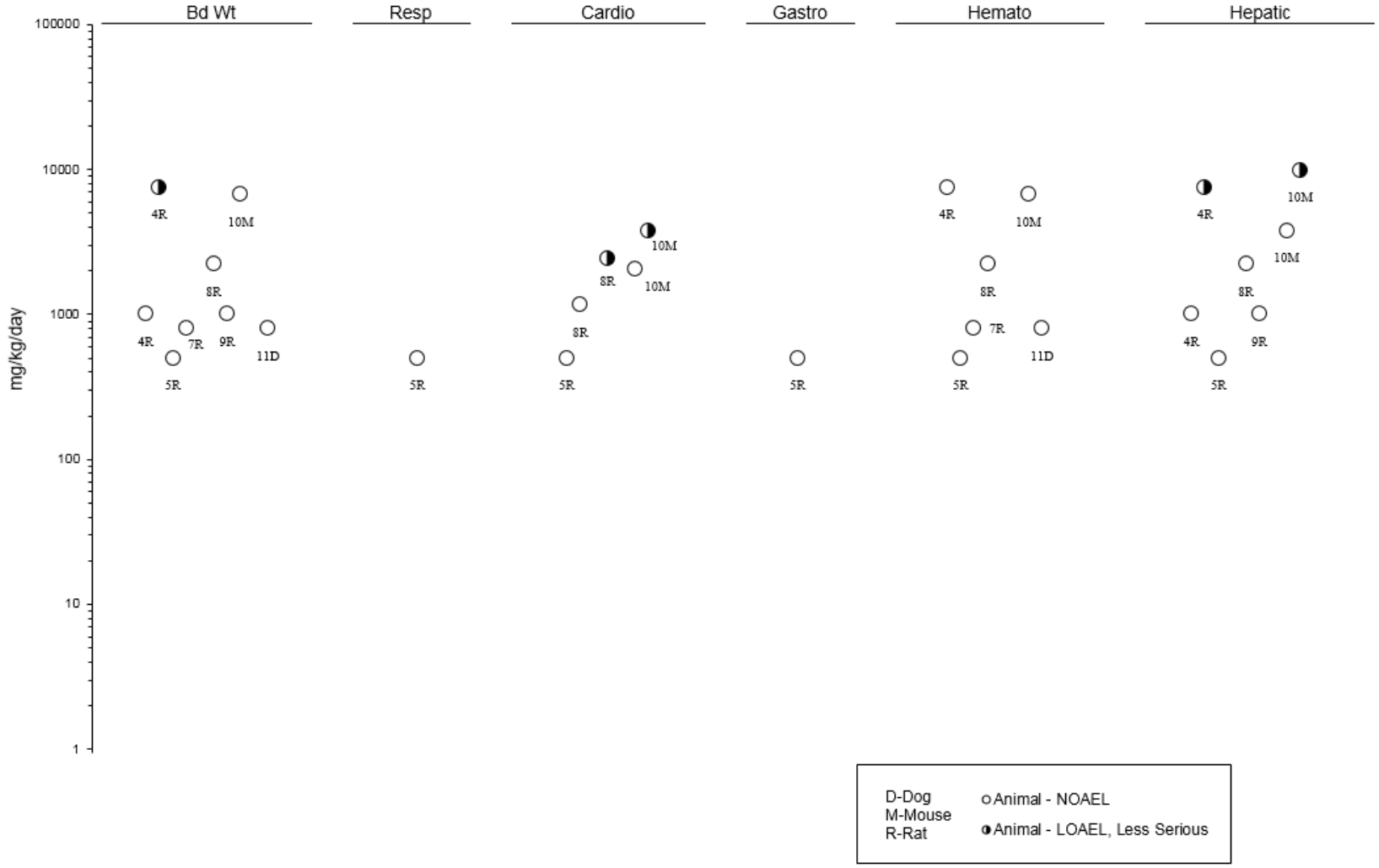


Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Intermediate (15-364 days)

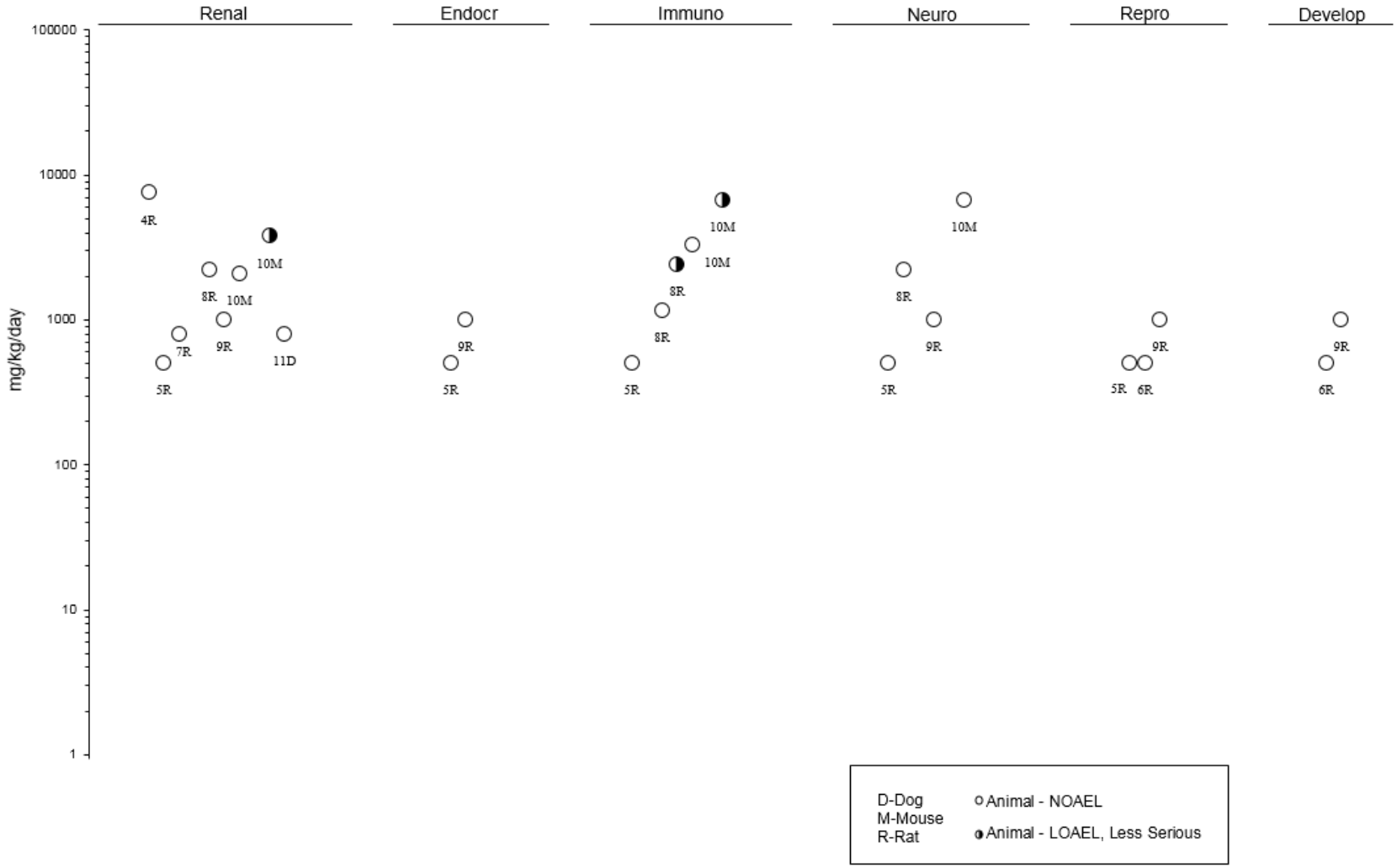
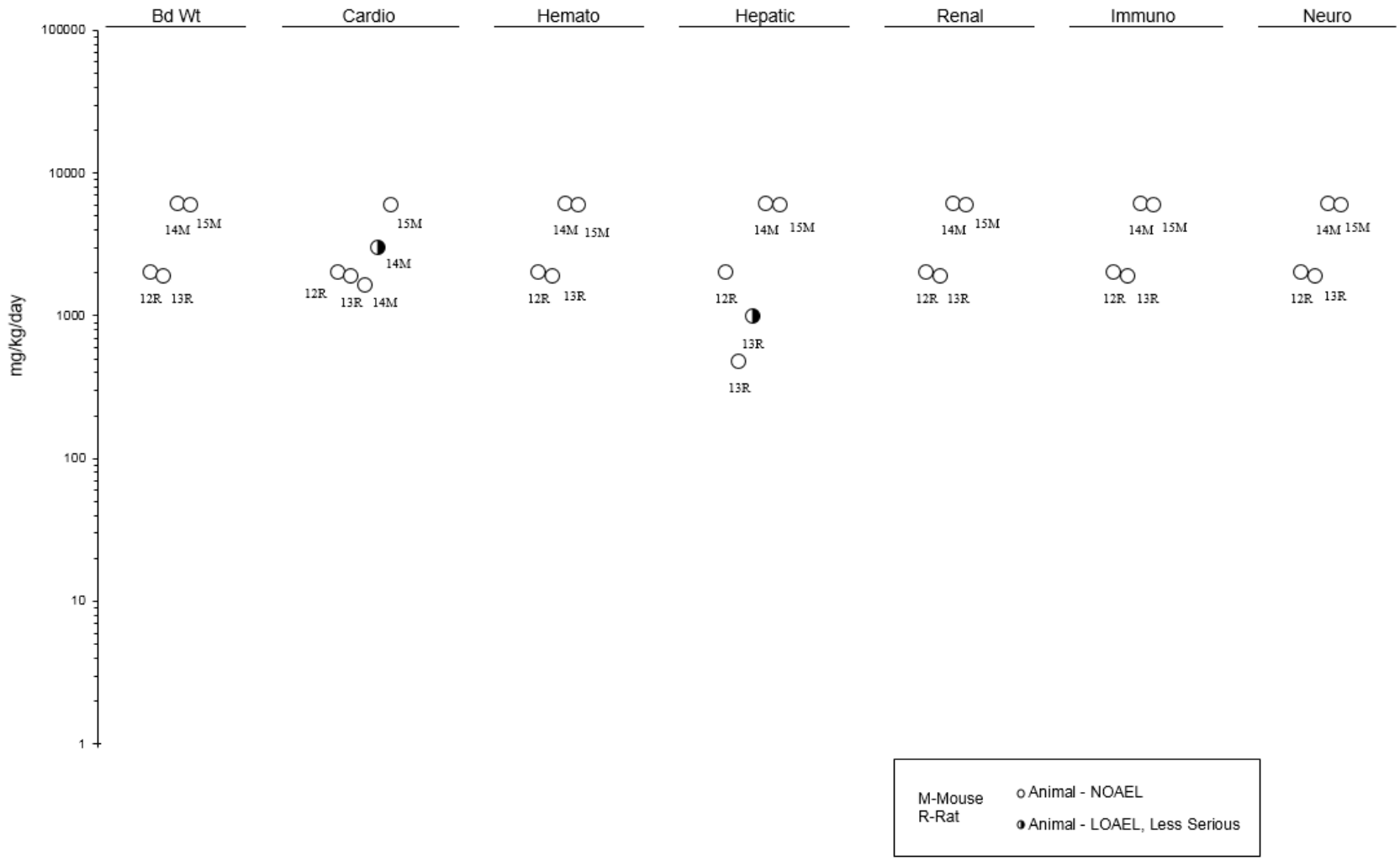


Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Chronic (≥365 days)



2.2 DEATH

Crystalline Silica, Inhalation. Prolonged occupational exposure has been associated with increased risk for silicosis and lung cancer, both of which can be lethal. Details are provided in Sections 2.4 (Respiratory) and 2.19 (Cancer).

Crystalline Silica, Oral. No studies evaluating mortality in humans following oral exposure to c-silica were identified. No mortalities were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg/day as sodium metasilicate in drinking water for 8 days (Öner et al. 2005, 2006). No mortalities were observed in guinea pigs exposed to 51 mg c-silica/kg/day as crushed quartz or granite in drinking water for 5 days/week for 4 months (Dobbie and Smith 1982).

Amorphous Silica, Inhalation. No studies evaluating death in humans following inhalation exposure to a-silica were identified. In the only animal study evaluating natural a-silica, 18/39 rabbits died within 9 weeks of exposure to raw diatomaceous earth (0% crystalline content) at dust levels of 124 mg/m^3 for 8 hours/day, 5 days/week (Tebbens et al. 1957). The study authors indicated that it was unclear if these deaths were attributable to exposure; however, no further deaths were observed when the dust levels were reduced to 60 mg/m^3 for the remaining 41 weeks of the study.

No mortalities were observed in an acute study in rats exposed to pyrogenic a-silica at 477 mg/m^3 for 4 hours (Lewinson et al. 1994). In a 2-week study in rats exposed to pyrogenic a-silica, 4/10 males and 2/10 females died following exposure to 209 mg/m^3 6 hours/day for 5 days/week; no mortalities were observed at ≤87 mg/m^3 (Reuzel et al. 1991). No deaths were observed in rats similarly exposed to precipitated a-silica at concentrations up to 668 mg/m^3 (Reuzel et al. 1991). In rats exposed to pyrogenic a-silica at 53 mg/m^3 8 hours/day for 5 days/week, a 74% mortality rate was reported by the study authors (Schepers et al. 1957a). However, the study authors also indicated that only one rat survived until scheduled sacrifice at 12 months (with three rats sacrificed each at 3, 6, and 9 months), suggesting 96% mortality in the main study group. The majority of unscheduled deaths occurred between 4 and 9 months; therefore, this study is reported as an intermediate-duration study in Table 2-1. No deaths occurred when rats were similarly treated for 1 month or guinea pigs were similarly treated for up to 24 months (Schepers et al. 1957a, 1957b). When rabbits were exposed to an unspecified synthetic a-silica compound (0% c-silica) for 8 hours/day, 5 days/week for up to 24 months, survival was ≤50% by 9 months at 130 mg/m^3 and by 3 months at 260 mg/m^3 (Schepers 1959).

In other studies, no treatment-related changes in survival were reported in laboratory animals (rats, rabbits, guinea pigs, and monkeys) exposed to various forms of synthetic a-silica for 6 hours/day, 5 days/week at concentrations up to 25 mg/m^3 for 1 week (Arts et al. 2007), 150 mg/m^3 for 4 weeks (Lee and Kelly 1992), 30 mg/m^3 for 13 weeks (Reuzel et al.1991), up to 9.9 mg/m^3 for up to 18 months (Groth et al. 1981), or 126 mg/m^3 for 8 hours/day, 7 days/week for 12–24 months (Schepers 1981).

Amorphous Silica, Oral. No studies evaluating mortality in humans following oral exposure to a-silica were identified. In an LD_{50} study in Sprague-Dawley rats, no deaths were observed during the 4-week observation period following single oral exposures to precipitated a-silica at doses up to 7,900 mg/kg via gavage in olive oil or pyrogenic a-silica at doses up to 5,000 mg/kg via gavage in peanut oil (Lewinson et al. 1994).

In an intermediate-duration dietary study in Wistar rats, 2/10 males and 2/10 females died during the 8th (and final) week of exposure to time-weighted average (TWA) pyrogenic a-silica doses of 7,500 mg/kg/day (Lewinson et al. 1994). Daily doses were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Mortalities were attributed to acute exposure to the highest administered dose of 16,000 mg/kg/day. Clinical signs of toxicity observed during weeks 6–8 included shyness, dirty fur, reduced activity, cachexia, and hemorrhage in the mucous membranes of the eyes and nose. No deaths were observed in rats exposed to dietary pyrogenic a-silica at doses up to 1,000 mg/kg/day for 5 weeks or 500 mg/kg/day for 6 months (Lewinson et al. 1994). Similarly, no exposure-related deaths were observed in F0 or F1 rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day for approximately 18 weeks (Wolterbeek et al. 2015). Mortality in F344 rats and B6C3F1 mice exposed to dietary a-silica gel for 6 months was comparable to controls at doses up to 2,413 and 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

In a 2-year bioassay, mortality in animals exposed to a-silica gel was similar to controls at dietary doses up to 2,010 mg/kg/day in F344 rats and 6,010 mg/kg/day in B6C3F1 mice (Takizawa et al. 1988). Similarly, mortality in Wistar rats exposed to pyrogenic a-silica at dietary doses of 100 mg/kg/day for 24 months was comparable to historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

2.3 BODY WEIGHT

Crystalline Silica, Oral. No studies evaluating changes in body weight in humans following oral exposure to c-silica were identified. No significant body weight effects were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg/day as sodium metasilicate in drinking water for 8 days, compared with controls (Öner et al. 2005, 2006); the baseline c-silica content in drinking water was 267 µg/L.

Amorphous Silica, Inhalation. No studies evaluating body weight effects in humans following inhalation exposure to a-silica were identified. In the only animal study evaluating natural a-silica, no body weight effects were noted in rabbits following exposure to raw diatomaceous earth (0% crystalline content) at dust levels of 72 mg/m^3 for 8 hours/day, 5 days/week for up to 50 weeks (Tebbens et al. 1957).

In 2-week concentration range-finding studies, decreased body weight gain was observed in rats exposed to synthetic a-silica 6 hours/day, 5 days/week at concentrations ≥44 mg/m^3 pyrogenic a-silica or 170 mg/m^3 precipitated a-silica, compared with controls (Reuzel et al. 1991); however, the biological significance of these findings is unclear as the magnitude of effect was not reported. In other studies, no body weight effects were observed in rats exposed for 6 hours/day, 5 days/week at concentrations up to 25 mg/m^3 pyrogenic, precipitated, or gel a-silica for 1 week (Arts et al. 2007), 150 mg/m^3 colloidal a-silica for 4 weeks (Lee and Kelly 1992), 30 mg/m^3 pyrogenic or precipitated a-silica for 13 weeks (Reuzel et al.1991), or up to 9.9 mg/m^3 pyrogenic, precipitated, or gel a-silica for up to 18 months (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating body weight effects in humans following oral exposure to a-silica were identified. In an LD_{50} study in Sprague-Dawley rats, no effects on body weight were observed during the 4-week observation period following single oral doses of precipitated a-silica at doses up to 7,900 mg/kg or pyrogenic a-silica at doses up to 5,000 mg/kg (Lewinson et al. 1994).

In an intermediate-duration study, mean body weight was decreased in male and female Wistar rats exposed to pyrogenic a-silica at TWA doses of 7,500 mg/kg/day for 8 weeks, compared with controls (Lewinson et al. 1994). Dose concentrations were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Body weight effects were observed during weeks 4–8. In other rat studies, no body weight effects were observed in CD rats exposed to silicon dioxide (unspecified) at dietary doses of 800 mg/kg/day for

4 weeks (Newberne and Wilson 1970) or Wistar rats exposed to pyrogenic a-silica at dietary doses up to 1,000 mg/kg/day for 5 weeks or 500 mg/kg/day for 6 months (Lewinson et al. 1994). Similarly, no body weight effects were observed in F0 or F1 adult 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). In mouse studies, no significant effects on body weight were observed in F344 rats or B6C3F1 mice exposed to a-silica gel at dietary doses up to 2,410 or 9,810 mg/kg/day, respectively, for 26 weeks (Takizawa et al. 1988). Additionally, no body weight effects were observed in Beagle dogs exposed to silicon dioxide (unspecified) at dietary doses of 800 mg/kg/day for 4 weeks (Newberne and Wilson 1970).

In a chronic-duration study, body weights in Wistar rats exposed to pyrogenic a-silica at dietary doses of 100 mg/kg/day for 24 months were comparable to historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant body weight effects were observed in F344 rats exposed to a-silica gel at dietary doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant body weight effects were observed following exposure to dietary a-silica (silicon dioxide) at doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

2.4 RESPIRATORY

Crystalline Silica, Inhalation.

Silicosis: Pathologic Features and Clinical Presentation. Unless otherwise noted, information in the following section was taken from these reviews: Akgun (2016); Bang et al. (2015); Beckett et al. (1997); Castrainova and Vallyathan (2000); Ding et al. (2002); EPA (1996); Fujimura (2000); Greaves (2000); Greenberg et al. (2007); IARC (1997); Kambouchner and Bernaudin (2015); Leung et al. (2012); Mossman and Churg (1998); Mossman and Glenn (2013); NIOSH (1986); NIOSH (2002); Peters (1986); Rimal et al. (2005); Steenland (2005); Steenland and Ward (2014); and Stratta et al. (2001a).

Silicosis is one of the oldest known occupational diseases, reported by ancient Greeks and Romans. It has only been observed following occupational exposure to respirable c-silica and not through exposure to c-silica in ambient air (Beckett et al. 1997; Steenland and Ward 2014). As stated by Steenland and Ward (2014), “while there is also some low-level c-silica exposure on beaches and in ambient air in general, there is no evidence such low-level exposure causes health effects.” 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 not under dispute. No other substances, including a-silica, are known to produce the unique pathological changes observed in silicosis. In the United States, despite improved industrial hygiene methods and more stringent recommended exposure limits, new cases of silicosis continue to be diagnosed. There is no known curative treatment for silicosis.

Silicosis is not a single disease entity, but is classified as different types: acute silicosis (also called silicoproteinosis or alveolar proteinosis), simple silicosis (also called chronic or nodular silicosis), progressive massive fibrosis (PMF) (also called conglomerate silicosis or complicated silicosis; a progression of simple silicosis), and accelerated silicosis (a rapidly progressive form of simple (chronic) silicosis). Type and severity of silicosis can be influenced by the intensity (frequently referred to as concentration), frequency, and duration of exposure. Cumulative c-silica dose, expressed as mg/m^3-year, is the most important factor in the development of silicosis. Silicosis can result in death due to respiratory failure. Time from first exposure to onset of disease (i.e., the latency period) varies inversely with intensity of exposure and may be as short as a few weeks for acute silicosis to as long as 20 or more years for simple silicosis and PMF. Due to the long latency period, patients may not be diagnosed until several years after exposure has ended. Disease severity may continue to slowly increase over decades even after exposure has been discontinued, possibly due to c-silica dust that is retained in the lung. Thus, cessation of exposure does not necessarily prevent development or progression of silicosis. Silicosis is diagnosed based on a known history of exposure to dust containing c-silica and radiographic findings, including the presence of nodules on chest radiograph or computed tomography (CT) scan, along with ruling out other diseases that may mimic silicosis (e.g., fungal infections, sarcoidosis). Pulmonary function tests are useful for determining severity, but not as useful as a diagnostic tool for silicosis as no pattern of lung function abnormality is specific for c-silica exposure or silicosis.

Simple silicosis. Simple silicosis, also called chronic or nodular silicosis, is the most common type of silicosis. It occurs following long periods (10–≥20 years) of continuous exposure to relatively low levels of c-silica dust, although “relatively low levels” has not been defined in quantitative terms. Simple silicosis can be either a restrictive, obstructive, or mixed lung disease characterized by diffuse, multiple nodular lesions in lung parenchyma and associated lymphoid tissue and lymph nodes, and fibrotic lesions of the pleura. Nodules, are typically small (≤1 mm in diameter) and more prominent in upper lobes of the lung; those in close proximity to small and medium airways cause narrowing and distortion of the airway lumen. Fibrotic nodules appear as concentric arrangements of whorled collagen fibers with central hyalinized zones; calcification and necrosis occur to varying degrees. Nodules also may contain c-silica

inclusions. Macrophages, fibroblasts, and lymphocytes are observed at the periphery of the nodules, and the pleura may appear thickened. Early in disease development, radiography typically shows small, round opacities of the upper lung. With disease progression, nodules become larger and denser and may be observed in the lower lung in more severe cases. Scarring and hypertrophy of bronchial-associated lymphoid tissue and intrapulmonary lymph nodes lead to compression of larger airways.

Early symptoms of simple silicosis are dyspnea on heavy exertion and dry cough; however, some patients may be asymptomatic. Pulmonary function and general health typically may not be compromised during the early stages. As the disease progresses, frequency and intensity of cough increases and sputum production may occur; dyspnea also occurs more frequently with less exertion. Decrements in lung function are often observed (e.g., nonreversible airflow obstruction, volume restriction, impaired gas exchange, pulmonary hypertension, right heart strain, and cor pulmonale), which may lead to right heart enlargement. In the later stages, hypoxemia may develop.

Progressive Massive Fibrosis (PMF). PMF, also called conglomerate silicosis or complicated silicosis, is a progression of simple silicosis. The factors that determine progression of simple silicosis to complicated silicosis have not been defined, but cumulative exposure and tuberculosis are risk factors. Complicated silicosis can develop after exposure to c-silica ceases.

Nodular lung lesions become larger (diameter >1–2 cm) and coalesce to form masses of hyalinized connective tissue, leading to destruction of the surrounding pulmonary architecture, including bronchioles and blood vessels. Necrosis and cavitation of lesions occur and PMF develops. Restricted lung volume, reduced pulmonary compliance, and poor gas exchange are observed. Compromised pulmonary function can lead to right ventricular failure, congestive heart failure, and increased risk of pneumothorax. General health significantly declines, and severe pulmonary damage can result in death.

Acute silicosis. Acute silicosis, also called silicoproteinosis or alveolar proteinosis, is a rapidly progressive alveolar filling disease associated with heavy, intense exposure (not quantitatively defined) to fine c-silica dusts, such as those generated during sandblasting, denim sand blasting, rock drilling, or milling and tunneling. The time to onset for acute silicosis varies from a few weeks to <10 years after the start of exposure, but most cases typically occur within 1–5 years. Acute silicosis frequently results in death due to respiratory failure. Like simple and complicated silicosis, acute silicosis progresses in the absence of further exposure.

Pathologically, acute silicosis is characterized by alveolar filling with an eosinophilic-granular, lipid-rich fluid containing debris from damaged cells, and interstitial inflammation with infiltration by neutrophils and alveolar macrophages containing lamellar bodies. Diffuse interstitial fibrosis often develops and extensive damage to the alveolar epithelium occurs. On radiography, diffuse alveolar opacification is observed in the middle and lower lobes.

Symptoms of acute silicosis include dyspnea, labored breathing, dry cough, decreased pulmonary function, compromised gas exchange, fever, fatigue, and weight loss. As the disease progresses, cyanosis and respiratory failure develop. Death from respiratory failure often occurs within a few months of the onset of symptoms.

Accelerated silicosis. Accelerated silicosis, associated with intense exposure to fine c-silica dusts, is a rapidly progressive form of simple (chronic) silicosis. It develops 5–10 years after the start of exposure and is typically associated with more moderate exposure (compared to simple silicosis). Symptoms are similar to those of simple silicosis. Accelerated silicosis is associated with significant morbidity and mortality.

Silicotuberculosis—a complication of silicosis. A complication of silicosis is superimposed pulmonary infection with mycobacteria or fungi. The most common form of infection in c-silica-exposed workers is tuberculosis (silicotuberculosis). The risk of tuberculosis infection increases with the severity of silicosis, although some occupational exposure studies have reported an increased risk of tuberculosis in c-silica workers in the absence of silicosis (Cowie 1994; teWaterNaude et al. 2006). Based on worker compensation claims in California during the period 1946–1979, Goldsmith et al. (1995) estimated the rate of death in males with silicotuberculosis as approximately 50 times greater than that of the general population. The prevalence of silicotuberculosis in the United States decreased with advances in tuberculosis drug therapy. However, due to the recent increase in drug-resistant tuberculosis, the potential for superimposed tuberculous infection in c-silica workers is a growing concern. The prevalence of silicotuberculosis is exacerbated by human immunodeficiency virus (HIV) epidemics, particularly in low-income countries (Rees and Murray 2007).

Silicosis Morbidity: Incidence and Exposure-Response Data. The current number of silicosis cases in the United States is not known (NIOSH 2002). 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. However, it is

likely that this incidence is underestimated due to the lack of a national surveillance system for silicosis (Steenland and Ward 2014). Recent surveillance data for silicosis showed no decrease in hospitalization due to silicosis in the United States over the time period 1993–2011 (Filios et al. 2015). The incidence of silicosis is higher in less-developed countries; for example, approximately 6,000 new cases of silicosis per year are diagnosed in China (Leung et al. 2012; Steenland and Ward 2014).

Several studies provide exposure-response data for silicosis incidence based on estimated cumulative exposure (expressed as mg/m^3-year) for various industries, including underground hardrock mining (Chen et al. 2001; Churchyard et al. 2004: Hnizdo and Sluis-Cremer 1993; Kreiss and Zhen 1996; Muir et al. 1989a, 1989b; Steenland and Brown 1995a), granite quarry mining and production (Ng and Chan 1994), diatomaceous earth mining and milling (Hughes et al. 1998; Park et al. 2002), and porcelain production (Mundt et al. 2011). Study details are provided in Table 2-4. These studies found that risk of silicosis increased with estimated cumulative exposure. However, risk estimates are not directly comparable across study designs that used different outcome metrics, follow-up periods, or statistical approaches to estimate risk. Another complication is that various industrial processes generate different types of c-silica particles (e.g., particle size, surface reactivity, fibrogenic potential) (see Section 2.20.2, Mechanisms of Toxicity; Section 4.2, Chemical and Physical Properties).

Chen et al. (2001) compared cumulative risks of silicosis for four hardrock mining cohorts (Chen et al. 2001; Hnizdo and Sluis-Cremer 1993; Kreiss and Zhen 1996; Steenland and Brown 1995a) (Figure 2-4). Relationships between estimated cumulative exposure and cumulative risks (estimated through the end of the follow-up periods) were similar across the cohorts, with each showing an increase in cumulative risk with increasing cumulative exposure. For a cumulative exposure of 4.5 mg/m^3-year (a 45-year exposure to 0.1 mg/m^3), cumulative risks ranged from approximately 55 to 90%. Cumulative risks will vary depending on length of follow-up period. Substantially lower risk estimates in a mining cohort were reported by Muir et al. (1989a, 1989b). For example, risks of 1 and 10% were associated with estimated cumulative exposures of 6.1 and 18.7 mg/m^3-year, respectively. However, it is possible that risks were underestimated due to the lack of a post-employment follow-up period (EPA 1996; NIOSH 2002). A study of a mining cohort published after Chen et al. (2001) showed that the incidence of silicosis significantly increased with cumulative exposure (p for trend <0.001) (Churchyard et al. 2004). For the highest estimated cumulative exposure category of 1.48–3.08 mg/m^3-year, the incidence of silicosis was 32%.

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Chen et al. 2001	Study design: retrospective cohort Industry: tin mining (four mines) Location: China	Cohort: 3,010 male (92.9%) and female tin miners employed for at least 1 year during 1960–1965, with follow-up through 1994 Adjustments: historical exposure information and task description of the job title Statistical analysis: Weibull model	Categories (C) for cumulative exposure to c-silica dust, calculated using reported cumulative total dust exposure and the mean c-silica dust concentration of 3.6% (midpoint): - C1: <0.36 (0.18) - C2: 0.36–0.72 (0.54) - C3: >0.72–1.4 (1.08) - C4: >1.4–2.2 (1.80) - C5: >2.2–2.9 (2.52) - C6: >2.9–3.6 (3.24) - C7: >3.6–5.4 (4.50) - C8: >5.4 (>5.4)	Silicosis cases: 1,015 (33.7% of cohort) Silicosis diagnosed post-exposure: 684 (67.4% of silicosis cases) Time after first exposure to onset of silicosis (mean±SD): 21.3±8.6 years Number of silicosis cases/workers in exposure group: - C1: 2/3,010 - C2: 24/2,677 - C3: 126/2,343 - C4: 127/1,717 - C5: 196/1,288 - C6: 141/902 - C7: 244/638 - C8: 155/221 Cumulative risk of silicosis (%): - C1: 0.10 - C2: 1.0 - C3: 7.0 - C4: 14.5 - C5: 28.5 - C6: 40.5 - C7: 66.3 - C8: 91.7 Lifetime risk exposure to 0.1 mg/m^3 for 45 years (4.5 mg/m^3-year): 55%

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Churchyard et al. 2004 (with some data reported in Collins et al. 2005)	Study design: cross-sectional Industry: gold mining Location: South Africa	Cohort: 520 current black gold miners, 37–60 years of age, recruited during November 2000 through March 2001; no follow-up period or assessment of previously employed miners Adjustments: none Statistical analysis: logistic regression	Cumulative exposure to respirable quartz: Mean±SD: 8.2±2.88 Median: 7.95 Range: 0–22.68 Categories (C) for cumulative exposure (mid-point): - C1: 0–0.80 (0.4) - C2: 0.80–0.99 (0.9) - C3: 0.99–1.24 (1.12) - C4: 1.24–1.48 (1.36) - C5: 1.48–3.08 (2.28) Duration of exposure (mean): 2.18 years	Silicosis cases: 93 (19%) Miners with silicosis per exposure group (%) (as reported in Collins et al. 2005): - C1: 11 (10.7) - C2: 8 (8.2) - C3: 18 (17.5) - C4: 23 (22.1) - C5: 33 (32.0) The prevalence of silicosis (%) significantly increased with cumulative exposure ($p<0.001$). Estimated prevalence of silicosis by cumulative exposure (number with silicosis/number workers in exposure category): - C1: 10.7 (11/103) - C2: 8.2 (8/97) - C3: 17.5 (18/103) - C4: 22.1 (23/104) - C5: 32.0 (33/103) For each unit increase for cumulative exposure (mg/m^3-year), the odds of silicosis increased by 3.2.

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Hnzido and Sluis-Cremer 1993	Study design: longitudinal retrospective Industry: gold mining Location: South Africa	Cohort: 2,235 white gold miners employed as underground gold miners from 1938 for at least 10 years, with follow-up to 1991 Adjustments: cumulative risk was adjusted for loss of workers who did not develop silicosis but whose exposure reached only a certain level (not specified); no adjustment was made for exposure to radon daughters in the mines Statistical analysis: cumulative risk calculated by Kaplan-Meier method	Cumulative respirable c-silica exposure (composed mainly of quartz and silicates, based on a 30% c-silica content in dust): Mean (SD): 6.6 (2.7) Range: 1.2–18.7 Cumulative exposure category (C) midpoints: - C1: 0.3 - C2: 0.9 - C3: 1.5 - C4: 2.1 - C5: 2.7 - C6: 3.3 - C7: 3.9 - C8: 4.5	Silicosis cases: 313 (14% of cohort) Number of silicosis cases/workers in exposure group: - C1: 0/2,218 - C2: 9/2,014 - C3: 48/1,540 - C4: 85/984 - C5: 93/515 - C6: 53/197 - C7: 20/55 - C8: 5/11 Silicosis risk increased exponentially with cumulative dust exposure. The increase in risk accelerated at the cumulative exposure category C4. Risk per unit of cumulative c-silica dust exposure [mean (SE)]: - C1: – - C2: 0.002 (0.001) - C3: 0.016 (0.002) - C4: 0.045 (0.005) - C5: 0.099 (0.010) - C6: 0.156 (0.021) - C7: 0.222 (0.048) - C8: 0.227 (0.060)

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Hughes et al. 1998	Study design: retrospective cohort Industry: diatomaceous earth industry Location: California	Cohort: 1,809 white workers in the diatomaceous earth industry with a minimum of 12 months of employment during 1942–1987; no follow-up period Adjustments: age Statistical analysis: Poisson regression	Categories for cumulative exposure to c-silica dust: - C1: ≤1 - C2: >1–≤3 - C3: >3–≤6 - C4: >6	Total silicosis cases: 81 (4.5%) Risk of silicotic opacities on radiography significantly increased with cumulative exposure (p for trend: <0.001). Relative risk (95% CI): - C1: 1 - C2: 4.35 (1.7, 11.06) - C3: 20.13 (8.2, 49.7) - C4: 40.37 (16.1, 101.3) Risks of radiographic opacities for cumulative exposure of 2.0 mg/m^3-year for dust concentrations: - <0.50 mg/m^3: 1.1% - >0.50 mg/m^3: 3.7% Risks of radiographic opacities for cumulative exposure of 4.0 mg/m^3-year for dust concentrations: - <0.50 mg/m^3: 3.3% - >0.50 mg/m^3: 12.4%
Kreiss and Zhen 1996	Study design: community-based random sample survey Industry: hard rock mining Location: Colorado	Cohort: 100 miners and 34 controls ≥40 years of age; range of follow-up period for individual miners: 0–56 years Adjustments: age, years since last exposure, packyears of smoking Statistical analysis: Logistic regression	Categories for cumulative c-silica exposure: - C1: 0 - C2: >0–1 - C3: >1–2 - C4: >2–3 - C5: >3	Prevalence of silicosis increased with cumulative exposure. Prevalence (%): - C1: 0 - C2: 12.5 - C3: 26.3 - C4: 55.6 - C5: 83.3

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Muir et al. 1989a,1989b	Study design: longitudinal retrospective cohort Industry: gold and uranium mining Location: Ontario	Cohort: 2,109 gold and uranium miners employed during the period 1940–1959, with follow-up to 1982 or end of exposure, whichever occurred first; no follow-up period. Adjustments: none reported Statistical analysis: Weibull model	Categories of cumulative exposure and numbers of miners in each category: - C1: 0–0.499 (1,313) - C2: 0.5–0.999 (582) - C3: 1.0–1.499 (103) - C4: 1.5–1.999 (48) - C5: >2.0 (63)	Silicosis cases: 32 Estimates of cumulative exposures [in mg/m^3-year (95% CI)] associated with risks of developing silicosis: - 1% risk: 6.1 (4.1, 8.9) - 2% risk: 8.5 (5.6, 12.8) - 5% risk: 13.2 (7.8, 22.5) - 10% risk: 18.7 (9.7, 36.1)
Mundt et al. 2011	Study design: epidemiological cohort Industry: porcelain manufacturing (100 plants) Location: Germany	Cohort: 17,644 workers (46.8% male) employed more than 6 months and participating in a screening program for silicosis in 1985–1987, with follow-up through 2005 Adjustments: age, sex, smoking Statistical analysis: Cox proportional hazards	Cumulative exposure to respirable c-silica: - ≤0.5 (referent) - >0.5–1.0 - >1.0–1.5 - >1.5–3.0 - >3 - ≤3 (referent) - >3–4 - >4–5 - >5–6 - >6	Cumulative exposure to >3 mg/m^3-year was associated with an increased risk of silicosis. Number of silicosis cases per cumulative exposure, not lagged: - ≤0.5 (referent): 4 - >0.5–1.0: 1 - >1.0–1.5: 2 - >1.5–3.0: 2 - >3: 31 - ≤3 (referent): 9 - >3–4: 1 - >4–5: 4 - >5–6: 6 - >6: 20 Silicosis hazard ratios (95% CI), not lagged: - ≤0.5: reference - >0.5–1.0: 0.3 (<0.1–2.6) - >1.0–1.5: 0.7 (0.1–3.8)

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
				- >1.5–3.0: 0.4 (0.1–2.2) - >3: 3.1 (1.1–9.3) - ≤3: reference - >3–4: 0.9 (0.1–7.5) - >4–5: 5.3 (1.6–17.3) - >5–6: 7.3 (2.6–20.8) - >6: 6.8 (3.0–15.3) Number of silicosis cases per cumulative exposure, lagged by 10 years: - ≤0.5 (referent): 5 - >0.5–1.0: 2 - >1.0–1.5: 1 - >1.5–3.0: 2 - >3: 30 - ≤3 (referent): 10 - >3–4: 3 - >4–5: 4 - >5–6: 4 - >6: 19 Silicosis hazard ratios (95% CI), lagged by 10 years: - ≤0.5: reference - >0.5–1.0: 0.7 (0.1–3.7) - >1.0–1.5: 0.4 (0.1–3.7) - >1.5–3.0: 0.5 (0.1–2.4) - >3: 3.7 (1.4–9.9) - ≤3: reference - >3–4: 2.9 (0.8–10.6) - >4–5: 4.9 (1.5–15.7) - >5–6: 5.2 (1.6–16.9) - >6: 6.7 (3.0–14.9)

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Ng and Chan 1994	Study design: cross-sectional Industry: granite industry Location: Hong Kong	Cohort: 206 current and 132 previous granite workers employed for at least 1 year in 1967–1985; decedents were not included; specific follow-up period was not specified Adjustments: age and smoking Statistical analysis: linear regression	Cumulative exposure to respirable quartz: <0.25–>10	Prevalence (%) of rounded opacities on x-ray for cumulative exposures: - <0.25: 0 - 0.25–<1.00: 0 - 1.00–<5.00: 12.77 - 5.00–<10.00: 25.00 - >10.00: 21.67 Prevalence (%) of irregular opacities on x-ray for cumulative exposures: - <0.25: 0 - 0.25–<1.00: 0 - 1.00–<5.00: 19.15 - 5.00–<10.00: 21.67 - >10.00: 46.31 Analysis by linear regression predicted risks of 6 and 8% for rounded and irregular opacities, respectively, for a 50-year-old worker with a cumulative exposure of 2.0 mg/m^3-year.
Park et al. 2002	Study design: historical cohort study Industry: diatomaceous earth mining and processing Location: California	Cohort: 2,342 white, male workers employed for at least 12 months during 1942–1994, with follow-up through 1994 Adjustments: calendar time, age, smoking, Hispanic ethnicity, time since first observation Statistical analysis: Poisson regression	Cumulative exposure to c-silica dust: - Mean: 2.16 - Maximum: 62.52	Workers diagnosed with silicosis: 70 Excess lifetime risk estimates (per 1,000 workers) for radiographic silicosis increased with increasing dust concentration (mg/m^3). Risk estimates were based on the assumption of exposure to a constant respirable c-silica concentration for 45 years.

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

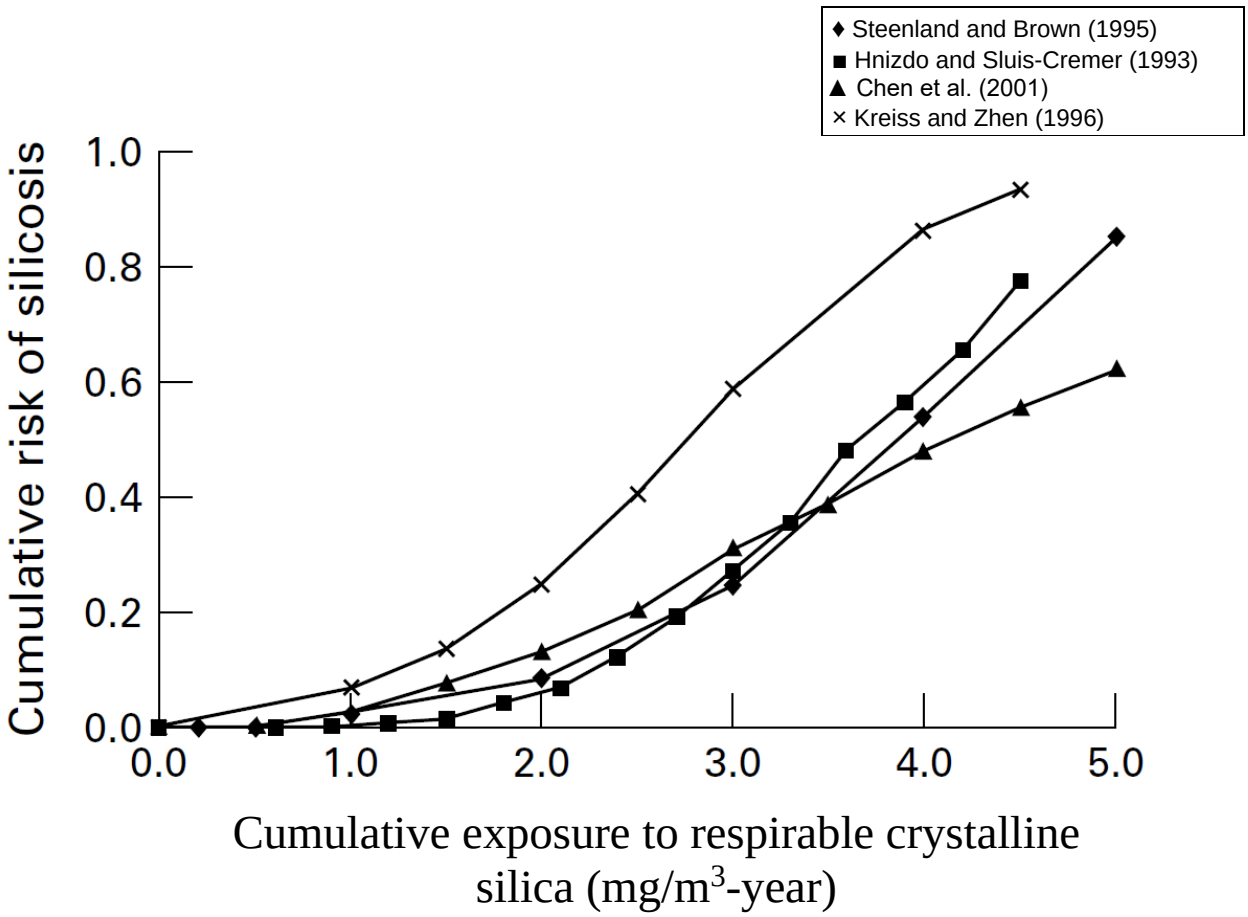
Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
				Excess lifetime risk (per 1,000 workers) for all cumulative exposures for respirable c-silica concentrations of: - 0.001: 6.2 - 0.005: 17.0 - 0.010: 26.0 - 0.020: 39.0 - 0.030: 50.0 - 0.040: 59.0 - 0.050: 68.0 - 0.060: 76.0 - 0.070: 83.0 - 0.080: 90.0 - 0.090: 96.0 - 0.100: 100.0 - 0.200: 150.0 Excess lifetime risk for cumulative exposures <10 mg/m^3-year for respirable c-silica concentrations of: - 0.001: 1.6 - 0.005: 7.8 - 0.010: 16.0 - 0.020: 31.0 - 0.030: 46.0 - 0.040: 60.0 - 0.050: 75.0 - 0.060: 89.0 - 0.070: 100.0 - 0.080: 120.0 - 0.090: 130.0 - 0.100: 140.0 - 0.200: 260.0

Table 2-4. Exposure-Response Data for Silicosis Morbidity in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Steenland and Brown 1995a	Study design: longitudinal retrospective cohort Industry: gold mining Location: South Dakota	Cohort: 3,330 white male underground gold miners employed for at least 1 year during 1940–1965, with follow-up through 1990; average exposure duration: 9 years Adjustments: age, calendar time Statistical analysis: Poisson regression	Cumulative exposure categories (midpoint): - C1: 0–0.2 (0.1) - C2: 0.2–0.5 (0.35) - C3: 0.5–1.0 (0.75) - C4: 1.0–2.0 (1.5) - C5: 2.0–3.0 (2.5) - C6: 3.0–4.0 (3.5) - C7: >4.0	Silicosis cases: 170 Number of silicosis cases/workers in exposure group: - C1: 5/3,330 - C2: 5/1,800 - C3: 15/1,060 - C4: 33/684 - C5: 44/331 - C6: 42/125 - C7: 26/52 Lifetime risk for each exposure category based on a 45-year exposure (first and second numbers of risk range are adjusted and unadjusted risks, respectively): - C1: 0.002 - C2: 0.005 - C3: 0.017–0.022 - C4: 0.060–0.084 - C5: 0.167–0.245 - C6: 0.403–0.534 - C7: 0.678–0.844 Estimated lifetime risk for exposure to 0.09–0.1 mg/m^3 for 45 years: 35–47%

CI = confidence interval; SD = standard deviation; SE = standard error

Figure 2-4. Cumulative Risk of Silicosis versus Estimated Cumulative Exposure to Respirable Crystalline Silica



Source: Reproduced from Chen et al. (2001) with permission from BMJ Publishing Group Ltd.

Similar risks were predicted for a cohort of granite workers, with predicted risks of 6 and 8% for rounded and irregular radiographic opacities, respectively, for an estimated cumulative exposure of 2.0 mg/m^3-year (Ng and Chan 1994). However, risks in this cohort may have been underestimated because decedents were not included.

In a study of white male diatomaceous earth workers, excess lifetime risk (extrapolated to age 85 years) of silicosis for a 45-year exposure to 0.1 mg/m^3 respirable silica was estimated to be 10% (Park et al. 2002). In a previous study of these workers, Hughes et al. (1998) estimated the risks of silicosis for a cumulative exposure of 2 mg/m^3-year of 1.1 and 3.7% for exposures to c-silica dust concentrations of <0.5 and >0.5 mg/m^3 respectively. For porcelain workers, risks for silicosis were significantly increased for cumulative exposures of ≥3 mg/m^3-year (Mundt et al. 2011). For a cumulative exposure range of 4–5 mg/m^3-year, lagged by 10 years (to account for latency period), the hazard ratio was 4.9 (95% CI: 1.5, 15.7) when combining all exposure categories <3.0 mg/m^3 as referent. Analysis of the Mundt et al. (2011) cohort using a threshold model estimated an exposure concentration threshold of 0.25 mg/m^3 (95% CI: 0.15, 0.30; Morfeld et al. 2013).

The estimated exposure-response data on silicosis reported in the studies above are briefly summarized in Table 2-5. 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). Churchyard et al. (2004) reported that at an estimated cumulative exposure range of 0–0.8 mg/m^3-year, 11/520 gold miners were diagnosed with silicosis. In summary, data from morbidity studies consistently demonstrate an exposure-response relationship between estimated cumulative exposure to respirable c-silica and silicosis over a wide range of exposure scenarios in several industries.

Silicosis Mortality: Exposure-Response Data. Progression of silicosis can result in death due to respiratory failure. There is considerable uncertainty regarding the number of annual deaths that occur worldwide due to silicosis. Driscoll et al. (2005) estimated that approximately 8,800 deaths per year that occurred worldwide were attributed to silicosis. The Global Burden of Disease Study (GBD 2015) estimated that 55,000 and 46,000 deaths occurred worldwide in 1990 and 2013, respectively. Based on data reported by 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 was a cause or contributing cause of 4,313 deaths in the United States during the period 1979–1990 (Althouse et al. 1995; Beckett et al. 1997). Due to improved industrial

Table 2-5. Summary of Exposure-Response Data for Silicosis Morbidity

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0–0.2	Silicosis cases/exposed workers: 5/3,330
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0–0.80	Silicosis cases/exposed workers: 11/103
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>0–1	Prevalence of silicosis (%): 12.5
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0.2–0.5	Silicosis cases/exposed workers: 5/1,800
Ng and Chan 1994	Granite	Cross-sectional	<0.25	Prevalence of silicosis (%): 0
Ng and Chan 1994	Granite	Cross-sectional	0.25–<1.00	Prevalence of silicosis (%): 0
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	0.3	Silicosis cases/exposed workers: 0/2,218
Chen et al. 2001	Tin mining	Retrospective cohort	<0.36	Silicosis cases/exposed workers: 2/3,010
Chen et al. 2001	Tin mining	Retrospective cohort	0.36–0.72	Silicosis cases/exposed workers: 24/3,010
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>0.5–1.0 (no lag)	HR (95% CI): 0.3 (<0.1–2.6)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>0.5–1.0 (10-year lag)	HR (95% CI): 0.7 (0.1–3.7)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	0.5–1.0	Silicosis cases/exposed workers: 15/1,060
Chen et al. 2001	Tin mining	Retrospective cohort	>0.72–1.4	Silicosis cases/exposed workers: 126/3,010
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0.80–0.99	Silicosis cases/exposed workers:8/97
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	0.9	Silicosis cases/exposed workers: 9/2,014
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	0.99–1.24	Silicosis cases/exposed workers:18/103

Table 2-5. Summary of Exposure-Response Data for Silicosis Morbidity

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.0–1.5 (no lag)	HR (95% CI): 0.7 (0.1, 3.8)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.0–1.5 (10-year lag)	HR (95% CI): 0.4 (0.1, 3.7)
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>1–2	Prevalence of silicosis (%): 26.3
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	1.0–2.0	Silicosis cases/exposed workers: 33/684
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>1–≤3	RR (95% CI): 4.35 (1.7, 11.06)
Ng and Chan 1994	Granite	Cross-sectional	1.00–<5.00	Prevalence of silicosis (%): 12.77
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	1.24–1.48	Silicosis cases/exposed workers: 23/104
Chen et al. 2001	Tin mining	Retrospective cohort	>1.4–2.2	Silicosis cases/exposed workers: 127/3,010
Churchyard et al. 2004 (as reported in Collins et al. 2005)	Gold mining	Cross-sectional	1.48–3.08	Silicosis cases/exposed workers: 33/103
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	1.5	Silicosis cases/exposed workers: 48/1,540
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.5–3.0 (no lag)	HR (95% CI): 0.4 (0.1, 2.2)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>1.5–3.0 (10-year lag)	HR (95% CI): 0.5 (0.1, 2.4)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	2.0–3.0	Silicosis cases/exposed workers: 44/331
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>2–3	Prevalence of silicosis (%): 55.6
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	2.1	Silicosis cases/exposed workers: 85/984

Table 2-5. Summary of Exposure-Response Data for Silicosis Morbidity

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Park et al. 2002	Diatomaceous earth	Historical cohort	2.16	Silicosis cases/exposed workers: 70/2,342
Chen et al. 2001	Tin mining	Retrospective cohort	>2.2–2.9	Silicosis cases/exposed workers: 196/3,010
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	2.7	Silicosis cases/exposed workers: 93/515
Kreiss and Zhen 1996	Gold and uranium mining	Longitudinal retrospective cohort	>3	Prevalence of silicosis (%): 83.3
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>3 (no lag)	HR (95% CI): 3.1 (1.1, 9.3)
Mundt et al. 2011	Porcelain	Epidemiological cohort study	>3.0 (10-year lag)	HR (95% CI): 3.7 (1.4, 9.9)
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	3.0–4.0	Silicosis cases/exposed workers: 42/125
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>3–≤6	RR (95% CI): 20.13 (8.2, 49.7)
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	3.3	Silicosis cases/exposed workers: 53/197
Chen et al. 2001	Tin mining	Retrospective cohort	>3.6–5.4	Silicosis cases/exposed workers: 141/3,010
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	3.9	Silicosis cases/exposed workers: 20/55
Steenland and Brown 1995a	Gold mining	Longitudinal retrospective cohort	>4.0	Silicosis cases/exposed workers: 26/52
Hnzido and Sluis-Cremer 1993	Gold mining	Retrospective longitudinal	4.5	Silicosis cases/exposed workers: 5/11
Ng and Chan 1994	Granite	Cross-sectional	5.00–<10.00	Prevalence of silicosis (%): 25.00
Chen et al. 2001	Tin mining	Retrospective cohort	>5.4	Silicosis cases/exposed workers: 155/3,010

Table 2-5. Summary of Exposure-Response Data for Silicosis Morbidity

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Hughes et al. 1998	Diatomaceous earth	Retrospective cohort	>6	RR (95% CI): 40.37 (16.1, 101.3)
Ng and Chan 1994	Granite	Cross-sectional	>10.00	Prevalence of silicosis (%): 21.67

CI = confidence interval; HR = hazard ratio; RR = rate-ratio

hygiene standards and more stringent regulatory standards and guidelines, silicosis mortality trends in the United States show a marked decline over the past 50 years (Bang et al. 2008, 2015). For example, in 1965, 1,065 deaths were attributed to silicosis compared to 165 deaths in 2004 (Bang et al. 2015). During the period 2001–2010, silicosis was identified as the underlying or contributing cause of 1,437 deaths, with 164 deaths (death rate: 0.74 per 1 million; 95% CI: 0.62, 0.85) in 2001 and 101 deaths (death rate: 0.39 per 1 million; 95% CI: 0.31, 0.47) in 2010 (p for trend =0.002) (Bang et al. 2015). However, estimates of the number of deaths in silicosis in the United States listed as a contributor in younger adults (ages 15–44 years) have not declined since 1995 (Mazurek and Attfield 2008). The reason for this is unknown; however, it has been speculated that contributing factors may include more recent, intense exposures, such as those associated with construction, abrasive blasting, and fracking industries (CDC 1998a, 1998b; Esswein et al. 2013; Mazurek and Attfield 2008).

Statistical modeling of estimated exposures and reported silicosis cases for occupational cohorts indicates that reported silicosis mortality rates are higher among workers with greater estimated cumulative exposure in several models (Checkoway et al. 1997; Chen et al. 2012; Hedlund et al. 2008; Hughes et al. 2001; McDonald et al. 2005; Park et al. 2002; Vacek et al. 2011). Study details are provided in Table 2-6. Results of these studies show statistically significant trends between estimated exposure and mortality rate and odds ratios (ORs) for workers exposed to c-silica in the diatomaceous earth, metal and ore mining, granite, pottery, and sand industries. A study of iron ore workers found that silicosis mortality increased with estimated cumulative exposure (Hedlund et al. 2008). Based on data from a cohort of white male U.S. diatomaceous earth workers, Park et al. (2002) estimated an excess lifetime risk of death from lung disease other than cancer of 54 per 1,000 (95% CI: 17, 150) for exposure to a c-silica dust concentration of 0.05 mg/m^3 over a working lifetime. The risk of radiographic silicosis was 75 per 1,000. Of 70 cases of silicosis incident during 1942–1994, 51 or 73% of cases occurred during the first 13 of 53 years (25%) of follow up (1942–1954). In Poisson regression models, radiographic silicosis incidence in the 1942–1954 period, controlling for cumulative exposure to silica, was 13.3 times higher than in subsequent years. The risk of radiographic silicosis was 75 per 1,000. As a reference, OSHA (1997) seeks to keep excess lifetime risks of serious disease below 1 per 1,000.

Results and details of pooled analyses on the relationship between c-silica exposure and silicosis mortality are summarized in Table 2-7 (Mannetje et al. 2000a, 2000b).

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Checkoway et al. 1997	Study design: historical cohort study Industry: diatomaceous earth mining and processing Location: California	Cohort: 2,342 white, male workers employed for at least 12 months during 1942–1987, with follow-up through 1994 Adjustments: age, calendar year, duration of follow-up, Hispanic ethnicity Statistical analysis: Poisson regression model	Cumulative exposure for respirable c-silica: - <0.5 (referent) - 0.5–<1.1 - 1.1–<2.1 - 2.1–<5.0 - ≥5.0	SMR for all deaths due to nonmalignant respiratory disease (except infections) was significantly increased. - Number of deaths: 67 - SMR (95% CI): 2.01 (1.56, 2.55). Deaths due to nonmalignant respiratory disease increased with cumulative exposure. Rate ratios (95% CI) lagged by 0 and 15 years to accommodate disease latency: 0-year lag: - <0.5 (reference): 7 [1] - 0.5–<1.1: 8 [1.52 (0.55, 4.20)] - 1.1–<2.1: 10 [1.98 (0.75, 5.22)] - 2.1–<5.0: 12 [2.34 (0.91, 6.00] - ≥5.0: 30 [4.79 (2.01, 11.9)] - Trend slope: 1.08 (1.03, 1.13) 15-year lag: - <0.5 (reference): 10 [1] - 0.5–<1.1: 9 [2.04 (0.77, 5.45)] - 1.1–<2.1: 8 [1.96 (0.71, 5.43)] - 2.1–<5.0: 13 [3.17 (1.25, 8.05)] - ≥5.0: 27 [5.35 (2.23, 12.8)] - Trend slope: 1.08 (1.03, 1.14)

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Chen et al. 2012	Study design: retrospective cohort study Industry: metal mines (tungsten, iron, copper, tin) and pottery factories Location: China	Cohort: 74,040 workers (85.8% males) employed for at least 12 months during 1960–1974, with follow-up through 2003; control: 24,731; low exposure: 15,438; medium exposure: 16,878; high exposure: 16,993 Adjustments: gender, year of hire, age at hire, type of mine/factory Statistical analysis: Cox proportional hazards regressions	Cumulative c-silica dust exposure: - Control: <0.01 - Low: 0.01–1.23 - Medium: 1.24–4.46 - High: >4.46	HR (95% CI) for death due to nonmalignant respiratory disease (p-value for positive trend: <0.001): - Control: 1 - Low: 1.89 (1.60, 2.24) - Medium: 4.28 (3.74, 4.91) - High: 6.68 (5.85, 7.61) HR increase for death due to nonmalignant respiratory disease per 1 mg/m^3-year increase in cumulative c-silica dust exposure: 1.069 (1.064, 1.074) SMR (95% CI) for death due to nonmalignant respiratory disease for the period 1970–2003: - 2.32 (2.24, 2.40)

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Hedlund et al. 2008	Study design: follow-up mortality study Industry: iron ore mining Location: Sweden	Cohort: 7,729 miners employed for at least 12 months during 1923–1996, with follow-up through 2001; control Adjustments: year of birth and attained age Statistical analysis: Poisson regression	Cumulative exposure quintiles for respirable quartz: - Q1: 0–0.9 (referent) - Q2: 1–2.9 - Q3: 3–4.9 - Q4: 5–6.9 - Q5: >7	Number of deaths from silicosis: 58 Adjusted mortality rate (per 100,000 person-years): - Q1: 18.7 - Q2: 32.8 - Q3: 117 - Q4: 129 - Q5: 140 Study authors stated that “cumulative respirable quartz exposure of approximately 3 mg/m^3-year and higher is associated with an increased risk of mortality due to silicosis.”

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Hughes et al. 2001	Study design: nested case referent study Industry: industrial sand plants (nine sand-producing plants) Location: North America	Cohort: (reported in McDonald et al. 2001) 2,670 men; employed before 1980 for at least 3 years with follow-up through 1994 Adjustments: smoking Statistical analysis: conditional logistic regression	Cumulative exposure quartiles for c-silica: For 0-year lag time: - Q1: ≤1.5 - Q2: 1.5–≤5.0 - Q3: >5.0–≤9.0 - Q4: >9.0 For 15-year lag time: - Q1: ≤0.7 - Q2: >0.7–≤1.8 - Q3: >1.8–≤5.1 - Q4: >5.1	Deaths from silicosis: 29 Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.03, one-tailed) was observed; mortality lagged for 15 years. Mortality ORs (95% CI not reported) lagged by 0 and 15 years to accommodate disease latency: 0-year lag: - Q1: 1 - Q2: 1.27 - Q3: 2.62 - Q4: 2.13 15-year lag: - Q1: 1 - Q2: 2.54 - Q3: 4.55 - Q4: 5.16
McDonald et al. 2005	Study design: historical cohort study with nested case-referent analysis Industry: industrial sand plants (eight sand-producing plants) Location: United States	Cohort: 2,452 male workers employed for at least 3 years, with ≥1 month during 1940–1979, with follow-up through 2000 Adjustments: case-referent analysis was adjusted for matching	Cumulative exposure quartiles for c-silica: For 0-year lag time: - Q1: ≤1.5 - Q2: 1.5–≤5.0 - Q3: >5.0–≤9.0 - Q4: >9.0 For 15-year lag time: - Q1: ≤0.7 - Q2: >0.7–≤1.8 - Q3: >1.8–≤5.1	Note: This study is an update of the cohort evaluated in Hughes et al. (2001), with an additional 5-year follow-up period and exclusion of workers from one Canadian plant. Deaths from nonmalignant respiratory disease: 116 SMR (nonmalignant respiratory disease): 164 (p<0.001)

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
		and three categories of smoking Statistical analysis: SMR: Poisson regression model Case-referent: conditional multiple logistic regression	- Q4: >5.1	Deaths from silicosis: 26 Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.017, one-tailed) was observed; mortality lagged for 15 years. Mortality ORs (95% CI not reported) lagged by 0 and 15 years to accommodate disease latency: 0-year lag: - Q1: 1 - Q2: 0.95 - Q3: 3.08 - Q4: 1.90 15-year lag: - Q1: 1 - Q2: 2.20 - Q3: 4.34 - Q4: 5.45

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Park et al. 2002	Study design: historical cohort study Industry: diatomaceous earth mining and processing Location: California	Cohort: 2,342 white, male workers employed for at least 12 months during 1942–1987, with follow-up through 1994 Adjustments: calendar time, age, smoking, Hispanic ethnicity, time since first observation Statistical analysis: Poisson regression model; lifetime risks of death from lung disease other than cancer (LDOC), excluding pneumonia and infectious diseases	Cumulative exposure to c-silica estimated for each worker using historical exposure data and detailed work history files. Mean: 2.16 Maximum: 62.52	Note: This is the same cohort reported in Checkoway et al. (1997), but with an additional 5-year follow-up period. Number of deaths due to LDOC: 67 Rate ratio at mean cumulative exposure: 4.2 ($p<0.0001$) Rate ratio at maximum cumulative exposure: 18.4 Rate ratio at a cumulative exposure of 1 mg/m^3-year: 1.55 Excess lifetime risk for white men exposed to 0.05 mg/m^3 for 45 years: 54/1,000 (95% CI: 17, 150)

Table 2-6. Exposure-Response Data for Mortality Due to Silicosis and Nonmalignant Respiratory Disease in Workers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Vacek et al. 2011	Study design: historical cohort study Industry: granite industry Location: Vermont	Cohort: 7,052 men employed in the Vermont granite industry from 1947 to 1998 Adjustments: 5-year age group, calendar year Statistical analysis: Poisson regression model	Cumulative exposure quintiles for respirable quartz: - Q1: ≤1.04 (referent) - Q2: 1.05–3.64 - Q3: 3.65–6.71 - Q4: 6.72–10.21 - Q5: >10.21	Number of deaths due to silicosis: 55 SMR (95% CI) for silicosis: 59.13 (44.55, 76.97); p≤0.01 Deaths due to silicosis increased with cumulative exposure. A statistically significant positive trend (p=0.001) was observed. Mortality ORs (95% CI); statistical significant relative to Q1: - Q1: 1 - Q2: 2.02 (0.45, 9.09); p=0.358 - Q3: 8.62 (1.86, 39.95). p=0.006 - Q4: 12.36 (2.67, 57.2); p=0.001 - Q5: 10.55 (2.30, 48.40); p=0.002

CI = confidence interval; HR = hazard ratio; OR = odds ratio; SMR = standardized mortality ratio

Table 2-7. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica

Reference	Cohorts	Methods	Outcomes for pooled cohort
Mannetje et al. 2002a	Six cohorts Checkoway et al. 1997: - Diatomaceous earth workers: 2,342 - Location: United States - Deaths due to silicosis: 15 - Mean exposure duration (years): 4.3 - Mean cumulative exposure (mg/m^3-year): 1.05 Koskela et al. 1994 - Granite workers: 1,026 - Location: Finland - Deaths due to silicosis: 14 - Mean exposure duration (years): 9.2 - Mean cumulative exposure (mg/m^3-year): 4.63[a] Costello and Graham 1988 - Granite workers: 5,408 - Location: United States - Deaths due to silicosis: 43 - Mean exposure duration (years): 18.0 - Mean cumulative exposure (mg/m^3-year): 0.71[a] Steenland et al. 2001a - Industrial sand workers: 40,27 - Location: United States - Deaths due to silicosis: 15 - Mean exposure duration (years): 3.7 - Mean cumulative exposure (mg/m^3-year): 0.13[a] Steenland and Brown 1995b - Gold miners: 3,348 - Location: United States - Deaths due to silicosis: 39 - Mean exposure duration (years): 5.4 - Mean cumulative exposure (mg/m^3-year): 0.23[a]	Study type: Pooled exposure-response analysis for mortality due to silicosis or unspecified pneumoconiosis Adjustments: Poisson regression: age, calendar period, original study cohort Nested case-control: age, sex, date of birth, original cohort study Literature search dates: not reported Statistical analysis: Poisson regression for standard life table analysis using 10 cumulative exposure categories; conditional logistic regression for nested case-control analysis Exposure for pooled cohort: - Mean exposure duration (years): 10.4 - Mean cumulative exposure (mg/m^3-year): 0.62	Total number of workers in pooled cohort: 18,364 Deaths due to silicosis: 150 Deaths due to pneumoconiosis: 20 Age of death (range): 32–91 years Silicosis mortality: 28.8 per 100,000 person years Adjusted mortality rate (per 100,000 person years) for cumulative c-silica exposures (mg/m^3-year): - 0–0.99: 4.7 - 0.99–1.97: 15.9 - 1.97–2.87: 29.2 - 2.87–4.33: 44.2 - 4.33–7.12: 64.3 - 7.12–9.58: 106.4 - 9.58–13.21: 112.6 - 13.21–15.89: 189.2 - 15.89–28.10: 118.0 - >28.10: 299.1 Adjusted mortality rate ratio (95% CI) for cumulative c-silica exposures (mg/m^3-year): - 0–0.99: 1.00 (referent) - 0.99–1.97: 3.39 (1.42, 8.08) - 1.97–2.87: 6.22 (2.56, 15.12) - 2.87–4.33: 9.40 (3.71, 23.80) - 4.33–7.12: 13.69 (5.04, 37.18) - 7.12–9.58: 22.64 (7.88, 65.10) - 9.58–13.21: 23.97 (8.05, 71.32) - 13.21–15.89: 40.25 (13.25, 122.3) - 15.89–28.10: 25.11 (8.09, 77.91) - >28.10: 63.63 (19.87, 203.8)

Table 2-7. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica

Reference	Cohorts	Methods	Outcomes for pooled cohort
	de Klerk and Musk 1998 - Gold miners: 2,213 - Location: Australia - Deaths due to silicosis: 44 - Mean exposure duration (years): 26.8 - Mean cumulative exposure (mg/m^3-year): 11.37[a]		Rate ratio (95% CI%) for nested case control analysis for an increase of one unit of exposure measure: - Cumulative exposure (mg/m^3-year): 1.04 (1.03, 1.06) - Log transformed cumulative exposure (log mg/m^3-days): 2.08 (1.71, 2.53) - Average exposure rate over working period (mg/m^3): 2.77 (1.80, 4.26) - Exposure duration (years): 1.04 (1.02, 1.06) Cumulative risk of death for exposure from ages 20 to 65 years for concentrations of: - 0.1 mg/m^3 (equivalent to 4.5 mg/m^3-year): 13 per 1,000 - 0.05 mg/m^3 (equivalent to 2.25 mg/m^3-year): 6 per 1,000
Mannetje et al. 2002b	Studies (n=29) by location and industry: - United States, diatomaceous earth workers (Checkoway et al. 1993, 1996a, 1997; Seixas et al. 1997) - Finland, granite workers (Koskela 1995; Koskela et al. 1987a, 1987b, 1994) - United States, granite workers (Costello and Graham 1988; Davis et al. 1983; Eisen et al. 1984; Theriault et al. 1974) - United States, industrial sand workers (Steenland et al. 2001a) - China, pottery workers (Chen et al. 1992; Dosemeci et al. 1993; McLaughlin et al. 1992)	Study type: Pooled exposure-response analysis for mortality due to silicosis, by location and industry Literature search dates: not reported Adjustments: not reported for overall cohorts Statistical analysis: conditional logistic regression	Pooled cohort Total number of workers: 65,980 OR (95% CI) for quintiles: - Q1: 1.0 - Q2: 3.1 (2.5, 4.0) - Q3: 4.6 (3.6, 5.9) - Q4: 4.5 (3.5, 5.8) - Q5: 4.8 (3.7, 6.2) SRRs and p-value for trend for silicosis mortality for exposure quartiles by cohort: C1[b]: p<0.001 C2[b]: p<01001 C3: - Q1: 1.00 - Q2: 2.02

Table 2-7. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica

Reference	Cohorts	Methods	Outcomes for pooled cohort
	- South Africa, gold miners (Hnizdo and Murray 1998; Hnizdo and Sluis-Cremer 1991, 1993; Hnizdo et al. 1997; Page-Shipp and Harris 1972; Reid and Sluis-Cremer 1996) - United States, gold miners (Brown et al. 1986; Steenland and Brown 1995a, 1995b; Zumwalde et al. 1981) - Australia, gold miners (de Klerk and Musk 1998; de Klerk et al. 1995; Hewson 1993) 10 occupational cohorts (C) identified from the studies above (number of workers): C1: United States, diatomaceous earth workers (2,342) C2: Finland, granite workers (1,026) C3: United States, granite workers (5,408) C4: United States, industrial sand workers (4,027) C5: China, pottery workers (9,017) C6: China, tin miners (7,858) C7: China, tungsten miners (28, 481) C8: South Africa, gold miners (2,260) C9: United States, gold miners (3,348) C10: Australia, gold miners (2,213)	Exposure: cumulative exposure (mg/m^3-year; median) quintiles for pooled cohort: Q1: not reported Q2: 4.45 Q3: 9.08 Q4: 16.26 Q5: 42.33 Respirable c-silica (mg/m^3; median; maximum) by cohort : C1: 0.18; 2.43 C2: 0.59; 3.60 C3: 0.05; 1.01 C4: 0.04; 0.40 C5: 0.22; 2.10 C6: 0.19; 1.95 C7: 0.32; 4.98 C8: 0.19; 0.31 C9: 0.05; 0.24 C10:0.43; 1.55 Cumulative exposure (mg/m^3-year; median, maximum) by cohort: C1: 1.05, 62.71 C2: 4.63, 100.98 C3: 0.71, 50.00 C3: 0.13, 8.265 C5: 6.07, 63.16 C6: 5.27, 83.09 C7: 8.56, 232.26 C8: 4.23, 9.28	- Q3: 1.23 - Q4: 4.14 - p=0.10 C4: - Q1: 0 - Q2: 1.22 - Q3: 2.91 - Q4: 7.39 - p<0.00001 C5: - Q1:34.8 - Q2: 4.13 - Q3: 44.3 - Q4: 77.3 - p<0.0001 C6: - Q1: 1.62 - Q2: 7.81 - Q3: 11.2 - Q4: 6.21 - p=0.05 C7: - Q1: 31.6 - Q2: 53.2 - Q3: 73.0 - Q4:69.1 - p=0.02 C8: SRRs could not be calculated because no deaths were coded to silicosis as the underlying cause C9[b]: p=0.10 C10: - Q1: 1.00 - Q2: 1.97 - Q3: 4.06

Table 2-7. Pooled Analyses on the Exposure-Response Relationship for Mortality due to Silicosis in Workers Exposed to c-Silica

Reference	Cohorts	Methods	Outcomes for pooled cohort
		C9: 0.23, 6.20 C10: 11.37, 50.22	- Q4: 4.23 - p<0.001

[a]Exposures were estimated by Mannetje et al. (2002b) (not reported in original publication), based on data provided by the original investigators.
[b]SRRs cannot be calculated as there were no deaths in the lowest exposure quartile; trend test can be conducted.

CI = confidence interval; OR = odds ratio; SRR = standardized rate ratio

Mannetje et al. (2002b) conducted a pooled analysis of 65,980 workers from 10 cohorts from the diatomaceous earth, granite, sand, mining, and pottery industries. The risk of death was increased for all estimated exposure levels (range: 4.45–42.33 mg/m^3-years), with standardized risk ratios ranging from 3.1 (95% CI: 2.5, 4.0) to 4.8 (95% CI: 3.7, 6.2) (Mannetje et al. 2002b). Similar results were observed in a pooled analysis of 18,364 workers from six cohorts from the diatomaceous earth, granite, sand, and mining industries (Mannetje et al. 2002a). Mannetje et al. (2002a) pooled data from six of the cohorts evaluated in the Mannetje et al. (2002b) study; however, four cohorts were excluded because of a different classification of disease for silicosis, which included silicosis, pneumoconiosis, and silicotuberculosis.

The adjusted estimated silicosis mortality rate increased from 4.7 per 100,000 person years for the lowest (non-referent) estimated exposure category (0–0.99 mg/m^3-year) to 299.1 per 100,000 person years for the highest estimated exposure category (>28 mg/m^3-year). The adjusted rate ratio increased with increasing estimated exposure and was significantly increased for all exposure categories, ranging from 3.39 to 63.63 in the 0.99–1.97 and >28 mg/m^3-year categories, respectively. The study authors estimated risks of death through age 65 for a 45-year exposure to 0.1 and 0.05 mg/m^3 to be 13 per 1,000 and 6 per 1,000, respectively.

Exposure-response data (based on estimated exposure data) on silicosis mortality reported in the studies discussed above are summarized in Table 2-8. Note that effect estimates in Table 2-8 generally are not comparable to each other, as reference groups differ. At the lowest reported estimated cumulative exposure range of 0.01–1.23 mg/m^3-year, risk of death due to silicosis in 74,040 metal miners and potters was increased by approximately 90% (hazard ratio [HR]: 1.89; 95% CI: 1.60, 2.24) (Chen et al. 2012). At the next highest estimated cumulative exposure range of 0.5–<1.1 mg/m^3-year, eight silicosis-related deaths were reported in 2,342 diatomaceous earth workers, although the rate ratio (RR: 1.52 [95% CI: 0.55, 4.20]) did not indicate an increase in risk (Checkoway et al. 1997). Data summarized in Table 2-8 are from several different silica industries and, therefore, it is likely that that differences in study methods, exposure settings, or other external factors may explain risk differences between and within industries. However, overall, these data demonstrate that the risk of death due to silicosis increases with cumulative exposure to respirable c-silica.

Table 2-8. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Chen et al. 2012	Metal mining; pottery	Retrospective cohort	0.01–1.23	HR: 1.89 (1.60, 2.24)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	0.5–<1.1 (0 lag time)	Number of deaths: 8/2,342 RR (95% CI): 1.52 (0.55, 4.20)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	0.5–<1.1 (15-year lag)	Number of deaths: 9/2,342 RR (95% CI): 2.04 (0.77, 5.45)
Hughes et al. 2001	Sand plants	Nested case referent	>0.7–≤1.8 (15-year lag)	OR[a]: 2.54
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	0.99–1.97	RR (95% CI): 3.39 (1.42, 8.08)
Vacek et al. 2011	granite	historical cohort study	1.05–3.64	OR: 2.02 (0.45, 9.09); p=0.358
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	1.1–<2.1 (0 lag time)	Number of deaths: 10/2,342 RR (95% CI): 1.98 (0.75, 5.22)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	1.1–<2.1 (15-year lag)	Number of deaths: 8/2,342 RR (95% CI): 1.96 (0.71, 5.43)
Chen et al. 2012	Metal mining	Retrospective cohort	1.24–4.46	HR: 4.28 (3.74, 4.91)
Hughes et al. 2001	Sand plants	Nested case referent	1.5–≤5.0 (0 lag time)	OR[a]: 1.27
Hughes et al. 2001	Sand plants	Nested case referent	>1.8–≤5.1 (15-year lag)	OR[a]: 4.55
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	1.97–2.87	RR (95% CI): 6.22 (2.56, 15.12)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	2.1–<5.0 (0 lag time)	Number of deaths: 12/2,342 RR (95% CI): 2.34 (0.91, 6.00)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	2.1–<5.0 (15-year lag)	Number of deaths: 13/2,342 RR (95% CI): 3.17 (1.25, 8.05)
Park et al. 2002	Diatomaceous earth	Historical cohort	2.16	RR: 4.2 (p<0.0001)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	2.87–4.33	RR (95% CI): 9.40 (3.71, 23.80)
Vacek et al. 2011	granite	historical cohort study	3.65–6.71	OR: 8.62 (1.86, 39.95); p=0.006

Table 2-8. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	4.33-7.12	RR (95% CI): 13.69 (5.04, 37.18)
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	4.45	OR (95% CI): 3.1 (2.5, 4.0)
Chen et al. 2012	Metal mining	Retrospective cohort	>4.46	HR: 6.68 (5.85, 7.61)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	≥5.0 (0 lag time)	Number of deaths: 30/2,342 RR (95% CI): 4.79 (2.01, 11.9)
Checkoway et al. 1997	Diatomaceous earth	Historical cohort	≥5.0 (15-year lag)	Number of deaths: 27/2,342 RR (95% CI): 5.35 (2.23, 12.8)
Hughes et al. 2001	Sand plants	Nested case referent	>5.0–≤9.0 (0 lag time)	OR[a]: 2.62
Hughes et al. 2001	Sand plants	Nested case referent	>5.1 (15-year lag)	OR[a]: 5.16
Vacek et al. 2011	Granite	historical cohort study	6.72–10.21	OR: 12.36 (2.67, 57.2); p=0.001
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	7.12–9.58	RR (95% CI): 22.64 (7.88, 65.10)
Hughes et al. 2001	Sand plants	Nested case referent	>9.0 (0 lag time)	OR[a]: 2.13
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	9.58–13.21	RR (95% CI): 23.97 (8.05, 71.32)
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	9.08	OR (95% CI): 4.6 (3.6, 5.9)
Vacek et al. 2011	Granite	historical cohort study	>10.21	OR: 10.55 (2.30, 48.40); p=0.002
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	13.21–15.89	RR (95% CI): 40.25 (13.25, 122.3)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	15.89–28.10	RR (95% CI): 25.11 (8.09, 77.91)
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	16.26	OR (95% CI): 4.5 (3.5, 5.8)
Mannetje et al. 2002a	Diatomaceous earth; granite; sand; gold mining	Pooled analysis	>28.10	RR (95% CI): 63.63 (19.87, 203.8)

Table 2-8. Summary of Exposure-Response Data for Death Due to Silicosis for Studies Reporting Risk Ratios, Hazard Ratios, or Odds Ratios

Reference	Industry	Study type	Estimated cumulative exposure (mg/m^3-year)	Outcome
Mannetje et al. 2002b	Diatomaceous earth; granite; sand; gold mining; pottery	Pooled analysis	42.33	OR (95% CI): 4.8 (3.7, 6.2)

[a]95% CI not reported.

CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio

In addition to the studies discussed above, numerous studies published since 1987 report significantly increased standardized mortality ratios (SMRs), mortality odds ratios, or hazard ratios for death due to silicosis and associated nonmalignant respiratory diseases, but do not report quantitative cumulative exposure estimates or exposure-response data specifically expressed in terms of mg/m^3-year (Bang et al. 2008; Brown et al. 1997; Calvert et al. 2003; Checkoway et al. 1993; Chen et al. 1992; Cherry et al. 2013; Chiyotani et al. 1990; Costello et al. 1995; Costello and Graham 1988; deKlerk and Musk 1998; deKlerk et al. 1995; Goldsmith et al. 1995; Koskela et al. 1987b, 1994; Marinaccio et al. 2006; Mehnert et al. 1995; Ng et al. 1990; Steenland and Brown 1995b; Thomas and Stewart 1987; Tse et al. 2007; Ulm et al. 2004; Zambon et al. 1987).

Decreased Lung Function in the Absence of Silicosis. Several studies have shown that occupational exposure to c-silica is associated with decreased in lung function in workers with no radiographic evidence of silicosis (Ehrlich et al. 2011; Hertzberg et al. 2002; Malmberg et al. 1993; Meijer et al. 2001; Mohner et al. 2013a, 2013b); see Table 2-9 for study details. In general, decrements in lung function are small and, while statistically significant, are of questionable clinical significance. Statistically significant trends ($p \leq 0.01$) were observed for decreased forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC in smokers in an automotive foundry; however, decreases from the lowest (<0.66 mg/m^3-year) to the highest (>5.9 mg/m^3-year) estimated exposure groups were small (approximately 9%). No effects on lung function were observed for nonsmokers in this cohort. In a cohort of granite industry workers, a statistically significant decrease in FEV_1/VC (vital capacity) was observed in workers compared to referents, although the decrease in workers was only 4% (Malmberg et al. 1993). Similarly, in concrete workers, a 2.2% decrease in FEV_1/FVC was statistically significant ($p=0.02$) (Meijer et al. 2001). Based on results of spirometry testing in a cohort of uranium miners, cumulative exposure to 1 mg/m^3-year was associated with a 2.75% decreased in FEV_1/FVC ($p<0.001$) and an increased risk of stage I COPD (OR: 1.81; 95% CI: 1.27, 2.56) (Mohner et al. 2013a, 2013b). Other studies showed similar small changes in lung function, although exposure data were not reported (Chia et al. 1992; Eisen et al. 1995).

Chronic Obstructive Pulmonary Disease (COPD). The American Thoracic Society defines COPD as a progressive lung disease involving the airways and/or pulmonary parenchyma, resulting in airflow obstruction that is not fully reversible (Qaseem et al. 2011). It manifests with a wide range of symptoms, including dyspnea, poor exercise tolerance, chronic cough with or without sputum production, and wheezing to respiratory failure or cor pulmonale (Qaseem et al. 2011). A diagnosis of COPD includes respiratory symptoms and airflow obstruction defined as postbronchodilator FEV_1:FVC ratio of

Table 2-9. Effects on Pulmonary Function Associated with Occupational Exposure to c-Silica in Workers with No Radiographic Evidence of Silicosis

Reference	Study design and industry	Cohort and methods	Estimated exposure (mg/m^3-year)	Outcome
Ehrlich et al. 2011	Study design: cross-sectional Industry: gold mining Location: South Africa	Cohort: 520 male, black gold miners; 37–60 years of age; mean years of service 21.8 (range: 6.3–34.5); number of workers with no evidence of radiographic silicosis reported Adjustments: smoking, tuberculosis, silicosis Statistical analysis: multivariate analysis	Cumulative respirable quartz (mg/m^3-year) - Mean (SD): 1.15 (0.44) - Median: 1.13 - Range: 0–3.08 Cumulative respirable dust (mg/m^3-year): - Mean (SD): 8.2 (2.90) - Median: 7.95 - Range: 0–22.68	For workers without silicosis in this cohort (based on cumulative dust data), for a 30-year exposure to a mean respirable dust concentration of 0.37 mg/m^3 (0.01 mg/m^3-year), the loss in FVC would be 208 mL (95% CI: 3, 412).
Hertzberg et al. 2002	Study design: cross-sectional Industry: automotive foundry Location: Midwestern United States	Cohort: 1,028 former (mean employment duration: 19.9 years) and current (18.3 years) workers, employed before 1986, with no radiographic evidence of silicosis Adjustments: weight, height, age, ethnicity, smoking status, other c-silica exposure Statistical analysis: logistic regression	Cumulative c-silica exposure quartiles (mg/ m^3-year; calculated from $mg/d/m^3$): - Q1: <0.66 - Q2: 0.66–2.0 - Q3: >2.0–5.9 - Q4: >5.9	In smokers, but not nonsmokers, percent predicted values for FVC, FEV_1, and FEV_1/FVC decreased with increasing exposure. Smokers FVC % predicted (SD): - Q1: 93.47 (11.85) - Q2: 90.54 (15.53) - Q3: 88.83 (13.43) - Q4: 84.36 (18.55) - p-value for trend: 0.0013 FEV_1 % predicted (SD): - Q1: 94.97 (14.85) - Q2: 92.58 (18.75) - Q3: 93.72 (15.88) - Q4: 85.24 (22.67) - p-value for trend: 0.011

Table 2-9. Effects on Pulmonary Function Associated with Occupational Exposure to c-Silica in Workers with No Radiographic Evidence of Silicosis

Reference	Study design and industry	Cohort and methods	Estimated exposure (mg/m^3-year)	Outcome
				FEV_1/FVC % predicted (SD): - Q1: 77.1 (7.2) - Q2: 77.7 (8.3) - Q3: 77.3 (6.4) - Q4: 70.4 (11) - p-value for trend: 0.0013 <u>Nonsmokers</u> FVC % predicted (SD): - Q1: 96.31 (10.56) - Q2: 94.1 (10.92) - Q3: 85.41 (23.06) - Q4: 89.89 (10.9) - p-value for trend: 0.1468 FEV_1 % predicted (SD): - Q1: 108.1 (15.15) - Q2: 100.31 (14.44) - Q3: 91.44 (22.87) - Q4: 97.29 (15.47) - p-value for trend; 0.1037 FEV_1/FVC % predicted (SD): - Q1: 79.6 (4.4) - Q2: 81.2 (3.9) - Q3: 76.2 (7.5) - Q4: 79.2 (4.7) - p-value for trend: 0.5696

Table 2-9. Effects on Pulmonary Function Associated with Occupational Exposure to c-Silica in Workers with No Radiographic Evidence of Silicosis

Reference	Study design and industry	Cohort and methods	Estimated exposure (mg/m^3-year)	Outcome
Malmberg et al. 1993	Study design: longitudinal study with 12-year follow-up Industry: granite industry Location: Sweden	Cohort: 45 granite crushers without pleural plaques and 45 age- and smoking-matched referents; pulmonary function evaluated in 1976 and 1988; mean exposure employment duration in 1988: 22 years Adjustments: none reported Statistical analysis: Wilcoxon's signed rank test, Mann-Whitney U test, multiple regression	Average respirable concentration (mg/m^3) 1976–1988: - Dust: 0.83 - c-Silica: 0.18 - Percent c-silica in dust: 23	Statistically significant differences in lung function values (percent predicted mean±SD) were observed for workers compared to referents for the FEV_1/VC, FEF_{50}, and Phase III (slope of alveolar flow). However, differences were very small and not are not likely to represent a clinically significant decrease. FEV_1/VC (%): - Referent: 76.2 (6.55) - Worker: 73.0 (9.45) - p-value: <0.01 FEF_{50}: - Referent: 5.1 (1.52) - Worker: 4.52 (1.82) - p-value: <0.05 Phase III: - Referent: 1.1 (0.63) - Worker: 1.45 (1.66) - p-value: <0.0.05

Table 2-9. Effects on Pulmonary Function Associated with Occupational Exposure to c-Silica in Workers with No Radiographic Evidence of Silicosis

Reference	Study design and industry	Cohort and methods	Estimated exposure (mg/m^3-year)	Outcome
Meijer et al. 2001	Study design: cross-sectional Industry: concrete Location: Netherlands	Cohort: 144 concrete workers with no radiographic evidence of silicosis (mean employment duration: 11.3 years) and 110 controls Adjustments: smoking, allergies Statistical analysis: multiple linear regression	Mean (SD) (mg/m^3-year) cumulative exposure: 0.566 (0.548)	No statistically significant increases in the prevalence of chronic respiratory symptoms (asthma, cough, phlegm, wheeze, and dyspnea) in workers compared to controls. A statistically significant increase was observed for work-related upper respiratory symptoms (WRURS) and work-related lower respiratory symptoms (WRLRS) for workers compared to controls. Percent with WRURS (SD): - Control: 7 (6.4) - Workers: 30 (20.8) - p=0.01 Percent with WRLRS (SD): - Control: 4 (3.6) - Workers: 17 (11.8) - p=0.02 A statistically significant (p=0.02) decrease was observed for FEV_1/FVC (%), although the difference was very small (2.2%) and not likely to be clinically significant. No differences were observed for FVC, FEV_1, or MMEF. OR (95% CI) for self-reported symptoms of COPD: 11.1 (2.8, 43.5)

Table 2-9. Effects on Pulmonary Function Associated with Occupational Exposure to c-Silica in Workers with No Radiographic Evidence of Silicosis

Reference	Study design and industry	Cohort and methods	Estimated exposure (mg/m^3-year)	Outcome
Mohner et al. 2013a, 2013b	Study design: nest case-control Industry: uranium mine Location: Germany	Cohort: 1,421 uranium miners born between 1954 and 1956 with no radiographic evidence of silicosis (mean employment duration: 12.8 years) Adjustments: smoking Statistical analysis: linear mixed regression	Cumulative exposure groups (EG) for respirable quartz (mg/m^3-year): - EG1: <0.1412 (referent) - EG2: 0.1412–0.2950 - EG3: 0.2950–0.5560 - EG4: 0.5560–0.9386 - EG5: 0.9386–1.2847 - EG6: >1.2847	ORs (95% CI) for incidence of stage I COPD (based on spirometry): - EG1: 1 - EG2: 1.83 (1.05, 3.19) - EG3: 2.65 (1.54, 4.58) - EG4: 2.47 (1.39, 4.38) - EG5: 1.78 (0.86, 3.69) - EG6: 3.83 (1.93, 7.57) Cumulative exposure to1 mg/m^3-year (respirable quartz) was calculated associated with a 2.75% decrease in FEV_1/FVC ($p<0.001$) and an increased OR for COPD (stage I) of 1.81 (95% CI: 1.27, 2.56).

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEF_{50} = forced mid-expiratory flow; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MMEF = maximal mid-expiratory flow; OR = odds ratio; SD = standard deviation; VC = vital capacity

<0.70 (Qaseem et al. 2011). Chronic obstructive pulmonary disease is associated with an abnormal inflammatory response to inhaled noxious gases, vapors, fumes, cigarette smoke, and respirable particulates, including c-silica (Brüske et al. 2014; Hnizdo and Vallyathan 2003; Qaseem et al. 2011).

Results of several occupational exposure studies show that COPD occurs in the presence and absence of radiological evidence of silicosis (Begin et al. 1995; Brüske et al. 2014; Cowie et al.1993; Ehrlich et al. 2011; Hertzberg et al. 2002; Hnizdo 1990; Hnizdo and Vallyathan 2003). A recent meta-analysis of six studies (Bakke et al. 2004; Hertzberg et al. 2002; Jorna et al. 1994; Malmberg et al. 1993; Meijer et al. 2001; Ulvestad et al. 2001) evaluated the association between occupational exposure to c-silica and COPD (Brüske et al. 2014). Statistically significant decreases in the mean difference of FEV_1 % predicted (-4.62; 95% CI: -7.17, -2.06) and the standard mean difference in FEV_1 (-0.27; 95% CI: -0.40, -0.14) were observed in workers exposed to c-silica dust compared to workers with "no/low" exposure. The standard mean difference of the FEV_1:FVC ratio also was significantly decreased in exposed workers compared to "no/low" exposure workers (-0.41; 95% CI: -0.54, -0.28). Results of this meta-analysis are consistent with COPD. However, it remains unclear if inhalation of c-silica produces pathological changes in the lungs that lead to the development of COPD or if COPD represents changes that lead to the development of silicosis (Hnizdo and Vallyathan 2003).

Lung Cancer. The association between occupational exposure to respirable c-silica and lung cancer is reviewed in Section 2.19.

Crystalline Silica, Oral. No studies evaluating respiratory effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. Human data are insufficient to determine whether or not a-silica is associated with lung disease in humans. Silicosis has not been observed in epidemiological studies in workers with long-term exposure to synthetic a-silica (precipitated or pyrogenic) and no known exposure to c-silica (Choudat et al. 1990; Plunkett and Dewitt 1962; Taeger et al. 2016; Volk 1960; Wilson et al. 1979). However, a German case-series study reported silicosis in 4/28 workers exposed to a non-specified form of a-silica that was not contaminated by quartz, although contamination by small amounts of cristobalite could not be ruled out (reviewed by Merget et al. 2002). A case-series report of ferrosilicon workers exposed to a-silica fume, which is primary 80% a-silica and 6–8% quartz, reported silicosis in only 1/10 cases reviewed (Swensson et al. 1971). In other studies of ferrosilicon workers, Vitums et al. (1977) reported pulmonary fibrosis in 11/40 workers exposed to a-silica fume, characterized

by reticular and/or nodular abnormalities in chest radiographs, and Robalo-Cordeiro et al. (1985) reported fibrosis in 9/14 workers exposed to a-silica fume.

Numerous occupational studies in the 1930s–1980s reported an increased incidence of pneumoconiosis in diatomaceous earth workers exposed to natural a-silica; however, the majority of reports indicated that co-exposure to cristobaline (c-silica) found in calcined diatomite was the primary cause of pneumoconiosis, rather than raw diatomite (which only contains trace amounts of 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). No evidence of pneumoconiosis was observed in potato workers exposed to inorganic dusts with high levels of diatomaceous earth and crystalline quartz (~10%) (Jorna et al. 1994).

Reduced pulmonary function has been reported in cross-sectional studies of workers exposed to a-silica; however, exposures to c-silica as well as other inorganic dusts were often present. Evidence for a potential link between a-silica and impaired lung function includes statistically significant ($p<0.05$) reduced forced expiratory flow volume in factory workers exposed to synthetic (precipitated) a-silica dust (Choudat et al. 1990), reduced FVC in factory workers exposed to synthetic (precipitated or pyrogenic) a-silica dust (Taeger et al. 2016), reduced FVC in grape workers exposed to mixed silica-dust containing both precipitated silica and diatomaceous earth (Gamsky et al. 1992), and reduced forced expiratory flow volume in potato workers exposed to inorganic dusts with high levels of diatomaceous earth and crystalline quartz (~10%) (Jorna et al. 1994). Decreased maximal breathing capacity, reduced timed vital capacity, and increased residual air were also reported in diamotite workers (Motley 1960; Motley et al. 1956). Additionally, dyspnea was observed in 9/14 ferrosilicon alloy workers in a case-series report (Robalo-Cordero et al. 1985). However, there was no correlation between cumulative dust exposure in 192 diatomaceous earth workers and lung function (Harber et al. 1998). Additionally, neither pulmonary function nor subjective complaints of respiratory symptoms were correlated with a calculated cumulative exposure index in a cohort of 165 workers exposed to synthetic precipitated a-silica for 1–35 years (Wilson et al. 1979, 1981). Lung function was also not impaired in three metallurgic workers diagnosed with pulmonary fibrosis that were exposed to a-silica fume (Vitums et al. 1977).

As reviewed below, available data from animal studies indicate that inhalation exposure to a-silica induces pulmonary toxicity, including pulmonary inflammation, granuloma formation, increased cellular infiltrates, and reduced lung function. Pulmonary effects observed following exposure to a-silica are generally reversible and no progressive fibrosis is observed, in contrast to pulmonary effects of c-silica.

Results of acute animal studies also indicate that different polymorphs of a-silica have different toxicological potencies, with precipitated and pyrogenic a-silica showing greater toxicity than a-silica gel and colloidal a-silica following acute exposure (Arts et al. 2007; Warheit et al. 1995). However, numerous polymorphs of a-silica exist, each with different surface chemistry properties and, therefore, different biological potencies (see Section 2.20.2 for additional details). In addition, as discussed in Section 4.2, even for the same polymorph, surface chemistry and, thereby, toxicological potency can vary based on production method and degree of hydration.

In the only animal study evaluating natural a-silica, thickening of the alveolar walls due to macrophage infiltration, accumulation of multinuclear cells with dust particles, and epithelization of the alveoli was observed in rabbits following exposure to raw diatomaceous earth (0% crystalline content) at TWA dust levels of 72 mg/m^3 for 8 hours/day, 5 days/week for 37–50 weeks (Tebbens et al. 1957). No lung fibrosis was observed in exposed rabbits.

Acute inhalation studies indicate that exposure to various synthetic a-silica polymorphs leads to inflammatory responses in the rat lung; however, the concentrations at which these effects occur can differ between polymorphs. Mild changes, including macrophage infiltration of lungs and lymphatic tissue and dilation of bronchioles and alveolar ducts, were observed in guinea pigs following a single 8-hour exposure to pyrogenic a-silica at 53 mg/m^3; after 24 hours of exposure, additional effects included alveolar hyperemia and focal petechiae, moderate bronchiole epithelial desquamation, and slight apical emphysema (Schepers et al. 1957b). In a repeat-exposure study with various polymorphs, elevated biomarkers of cytotoxicity and inflammation in bronchoalveolar lavage fluid, increased lung and tracheobronchial lymph node weights, and mild histopathological changes (accumulation of alveolar macrophages, bronchial/bronchiolar hypertrophy, and/or intra-alveolar granulocytic infiltrates) were observed in Wistar rats following exposure to precipitated or pyrogenic silica at ≥5 mg/m^3 for 5 days (6 hours/day), but effects following a 5-day exposure to silica gel were only observed at 25 mg/m^3 (Arts et al. 2007). Additionally, minor histopathological lesions (hyperemia and/or macrophage aggregates) persisted after recovery periods of 1–3 months following exposure to precipitated or pyrogenic silica, but not silica gel (Arts et al. 2007). These data indicate that silica gel is less potent than precipitated or pyrogenic silica under the same test conditions. More serious respiratory effects were observed in Wistar rats exposed to pyrogenic hydrophilic silica at 17 mg/m^3, pyrogenic hydrophobic silica at 31 mg/m^3, or precipitated hydrophobic silica at 46 mg/m^3 for 2 weeks (6 hours/day, 5 days/week), including respiratory distress, inflammation, pneumonia, granulomas, edema, increased cellularity, and/or increased lung weight (Reuzel et al. 1991). 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; the rationale for different concentration selection was not provided (Reuzel et al. 1991). In Crl:CD BR rats, exposure to colloidal silica for 2 weeks (6 hours/day, 5 days/week) at concentrations ≥50.5 mg/m^3, but not 10.1 mg/m^3, led to significantly elevated biomarkers of inflammation in bronchoalveolar lavage fluid; however, these changes were observed following only 3 days of exposure to precipitated silica at ≥10 mg/m^3 (6 hours/day), suggesting that precipitated silica is more potent than colloidal silica (Warheit et al. 1991, 1995).

Intermediate-duration inhalation studies also reported that exposure to precipitated, pyrogenic, or colloidal a-silica for 4 or 13 weeks (6 hours/day, 5 days/week) leads to inflammatory responses in the rat lung; however, available studies have limited information regarding direct comparison of potency across different polymorphs. In 4-week studies, colloidal a-silica led to elevated biomarkers of inflammation in bronchoalveolar lavage fluid, inflammation, and hyperplasia in Crl:DC BR rats at ≥50 mg/m^3, but not at 10 mg/m^3 (Lee and Kelly 1992; Warheit et al. 1991, 1995). In a 13-week study in Wistar rats, Reuzel et al. (1991) reported serious respiratory effects at the lowest tested concentrations for each polymorph tested (pyrogenic hydrophilic silica at ≥1 mg/m^3, pyrogenic hydrophobic silica at 30 mg/m^3, and precipitated hydrophobic silica at 30 mg/m^3). Observed effects for all polymorphs included increased lung weight and histopathological changes including increased cellularity, inflammation, accumulation/aggregation of alveolar macrophages (granulomas), and increased collagen content; however, focal interstitial fibrosis was only observed following exposure to pyrogenic hydrophilic silica (Reuzel et al. 1991). Focal interstitial fibrosis changes and increased collagen content persisted, but did not progress, up to 1 year following exposure to pyrogenic hydrophilic silica at concentrations ≥6 mg/m^3; for other polymorphs, increased cellularity, leukocytic infiltration, alveolar macrophage accumulation, and increased collagen content persisted for 13–39 weeks, but recovered by 1 year (Reuzel et al. 1991). Lung inflammation, proliferative responses, and alveolar septal fibrosis were also observed in F344 rats exposed to pyrogenic hydrophilic silica for 13 weeks (6 hours/day, 5 days/week) at 50.4 mg/m^3 (the only concentration tested); these findings decreased during the 8-month recovery period (Johnston et al. 2000).

Respiratory effects were also evaluated in a study designed to be chronic (12 months) with interim sacrifices (3, 6, and 9 months); however, due to high mortality resulting in only a single rat surviving until the 12-month sacrifice, this study is considered as an intermediate-duration study. In this study, macrophage infiltration, cellular nodules, and focal emphysema were observed in rats following exposure to pyrogenic a-silica at 53 mg/m^3 for 8 hours/day, 5 days/week for 3–9 months, with the single animal surviving at 12 months showing similar effects (Schepers et al. 1957a). Macrophage infiltration and

enlargement of lymphoid tissue were also reported. Near complete reversal of findings was observed in animals exposed for 6 months and allowed to recover for an additional 6 months (Schepers et al. 1957a). A companion study also evaluated respiratory effects in rabbits similarly exposed to pyrogenic a-silica at 53 mg/m^3, and observed similar pulmonary findings after 3–12 months of exposure (macrophage infiltration, cellular nodules, ductal stenosis, emphysema, collagen deposition, enlargement of pulmonary lymph nodes) (Schepers et al. 1957c). Exposed rabbits also showed dyspnea during physical exertion. As in the rat study, the majority of animals (70%) died prior to study termination and only 1/10 rabbits survived until the terminal sacrifice at 365 days; therefore, this study is also considered an intermediate-duration study. In similarly exposed guinea pigs, macrophage infiltration in the lungs and lymphoid tissue, alveolar vacuolation, alveolar and bronchiole stenosis, emphysema, and focal fibrosis were observed following exposure to pyrogenic a-silica at 53 mg/m^3 for 2–10 months (Schepers et al. 1957b). Rosenbrunch (1992) reported enlarged pulmonary lymphatic tissue and dust-laden macrophages in lung-associated lymph nodes following exposure to synthetic vitreous a-silica at 10.9 mg/m^3 for 4–12 months; however, only pulmonary lymph tissues were examined.

Chronic-duration studies also show adverse respiratory effects of synthetic a-silica; however, available studies only utilized a single exposure concentration (precluding a dose-response analysis). In monkeys, macrophage infiltration, emphysema, bronchiole and alveolar hypertrophy, stenosis, fibrosis, and slight collagen deposition were observed following exposure to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for 12 months (Schepers 1962). Another study in monkeys reported early nodular pulmonary fibrosis, characterized by macrophage and mononuclear cell aggregates and reduced lung function following exposure to a-silica (pyrogenic, precipitated, or gel) at 15 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months; respirable concentrations were reported as 9.9 mg/m^3 for pyrogenic a-silica, 6.9 mg/m^3 for precipitated a-silica, and 9.4 mg/m^3 for a-silica gel (Groth et al. 1981). Collagen fibers were observed in cell aggregates in lungs from monkeys exposed to pyrogenic a-silica, but total lung collagen content was not elevated; no treatment-related changes in lung collagen were observed in monkeys exposed to precipitated a-silica or a-silica gel. Pathological changes in the lungs were not observed in rats or guinea pigs similarly exposed for up to 12 months, compared with controls (Groth et al. 1981). Another chronic study reported increased lung weights and accumulation of macrophages in alveoli, bronchioles, and lymphoid tissue in rats, guinea pigs, and rabbits exposed to precipitated a-silica at 126 mg/m^3 for 8 hours/day, 7 days/week for 12–24 months; however, no epithelization or fibrosis were observed (Schepers 1981). Near-complete reversal of adverse effects was observed during a recovery period of 3–9 months. Macrophage infiltration in the lungs and lymphoid tissue, alveolar vacuolation, alveolar and bronchiole stenosis, emphysema, and pulmonary fibrosis were observed in guinea pigs

exposed to pyrogenic a-silica at 53 mg/m^3 for 8 hours/day, 5 days/week for 12–24 months; only partial reversal of adverse effects was observed during a recovery period of 1–12 months (Schepers et al. 1957b). Similar effects were observed in rabbits exposed to an unspecified synthetic a-silica compound (0% c-silica), with various pulmonary lesions (macrophage infiltration, stenosis, emphysema, sclerosis and epithelization, granulomatosis) and exertional dyspnea following exposure at ≥30 mg/m^3 for up to 24 months (Schepers 1959).

Amorphous Silica, Oral. No studies evaluating respiratory effects in humans following oral exposure to a-silica were identified. No significant changes in lung weight or histology were observed in Wistar rats exposed to pyrogenic a-silica at dietary doses of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). No changes in lung histology were observed in Wistar rats exposed to pyrogenic a-silica at dietary doses of 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

2.5 CARDIOVASCULAR

Crystalline Silica, Oral. No studies evaluating cardiovascular effects in humans following oral exposure to c-silica were identified. Changes in endothelial vasoactivity of the aorta were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg-day as sodium metasilicate in drinking water for 8 days, compared with controls; baseline c-silica content in drinking water was 267 µg/L (Öner et al. 2006). Observed changes included significantly ($p<0.05$) increased *ex vivo* contractile responses to phenylephrine and dilation responses to acetylcholine, sodium nitroprusside, and the calcium ionophore A-23187 in aortic rings isolated from exposed rats, compared with aortic rings isolated from controls. The toxicological significance of these findings is not known.

Amorphous Silica, Inhalation. No studies evaluating cardiovascular effects in humans following inhalation exposure to a-silica were identified. Cardiac hypertrophy was reported in monkeys exposed to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for 12 months (Schepers 1962). Hypertension and ventricular and auricular hypertrophy were reported in rabbits following exposure to an unspecified synthetic a-silica (0% c-silica) at dust levels ≥30 mg/m^3 for 8 hours/day, 5 days/week for 3–24 months (Schepers 1959). Hypertension was also reported in rabbits exposed to pyrogenic a-silica at 53 mg/m^3 for 8 hours/day, 5 days/week for 3–12 months; however, the biological relevance of the findings could not be assessed due to limited data reporting, low animal numbers, and high percentage of accidental animal death associated with cardiac puncture (Schepers et al. 1957c).

Amorphous Silica, Oral. No studies evaluating cardiovascular in humans following oral exposure to a-silica were identified. No significant changes in heart weight or histology were observed in Wistar rats exposed to pyrogenic a-silica (FHS) at dietary does of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). A significant 19% decrease in heart weight was observed in female B6C3F1 mice exposed to a-silica gel at dietary doses ≥3,780 mg/kg/day for 26 weeks; heart weights were not decreased in female B6C3F1 mice at 2,070 mg/kg/day, male B6C3F1 mice at doses up to 6,700 mg/kg/day, or F344 rats at doses up to 2,410 mg/kg/day (Takizawa et al. 1988). In the same study, no treatment-related changes in heart histology were reported in rats or mice exposed for 26 weeks at doses up to 2,410 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

In a 2-year dietary bioassay with a-silica gel, no significant changes in heart weight or histology were observed at doses up to 2,010 mg/kg/day in F344 rats or 6,010 mg/kg/day in B6C3F1 mice (Takizawa et al. 1988). However, in the 12-month interim sacrifice, a significant 13–18% decrease in heart weight was observed in female mice at ≥2,970 mg/kg/day; heart weights were not decreased in female mice at 1,640 mg/kg/day, male mice at doses up to 6,100 mg/kg/day, or rats at doses up to 2,220 mg/kg/day (Takizawa et al. 1988). No histopathological changes were observed in the heart at the 12-month interim sacrifice at doses up to 2,220 in rats or 7,560 mg/kg/day in mice (Takizawa et al. 1988).

2.6 GASTROINTESTINAL

Crystalline Silica, Oral. No studies evaluating gastrointestinal effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating gastrointestinal effects in humans following inhalation exposure to a-silica were identified. No treatment-related changes in gastrointestinal histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991) or monkeys exposed to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating gastrointestinal effects in humans following oral exposure to a-silica were identified. No histopathological changes were observed in the stomach, small

intestine, or large intestine of Wistar rats exposed to pyrogenic a-silica at dietary doses of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994).

2.7 HEMATOLOGICAL

Crystalline Silica, Oral. No studies evaluating hematological in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating hematological effects in humans following inhalation exposure to a-silica were identified. A significant 2–3-fold increase in neutrophil counts and slight increases in hemoglobin, packed cell volume, and erythrocyte counts were observed in rats exposed to pyrogenic a-silica at 30 mg/m^3 for 13 weeks (6 hours/day, 5 days/week), compared with controls, but not at concentrations ≤6 mg/m^3; after a 3-month recovery period, hematological parameters no longer differed from controls (Reuzel et al. 1991). Other acute- and intermediate-duration studies reported hematological changes following exposure to a-silica, including increased hemoglobin, packed cell volume, and erythrocyte count in rats exposed to pyrogenic or precipitated a-silica at ≥87 mg/m^3 for 2 weeks (Reuzel et al. 1991) and rabbits exposed to pyrogenic a-silica at 53 mg/m^3 for 3–12 months (Schepers et al. 1957c), and increased mean neutrophil count and hemoglobin levels and decreased mean lymphocyte count in rats exposed to colloidal a-silica at 150 mg/m^3 for 4 weeks (Lee and Kelly 1992); however, the biological relevance of the findings could not be assessed due to the absence of quantitative data reporting.

In a chronic study, rabbits exposed to precipitated a-silica at a concentration of 126 mg/m^3 for 8 hours/day, 7 days/week for 12 months showed a 22% increase in erythrocyte counts, a 40% increase in hemoglobin levels, and a 12% increase in packed cell volume, compared with controls (Schepers 1981). Increased levels persisted to some degree after a 12-month recovery period. These findings are consistent with an adaptive response to observed cardiopulmonary distress in exposed rabbits, rather than evidence of an adverse hematological response to silica exposure. No treatment-related changes in hematological parameters were observed in monkeys, rats, or guinea pigs following exposure to fumed, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating hematological effects in humans following oral exposure to a-silica were identified. No changes in hemoglobin, packed cell volume, prothrombin time, or total or differential leukocyte counts were observed in Beagle dogs or CD rats exposed to silicon dioxide

(unspecified) at dietary doses of 800 mg/kg/day for 4 weeks (Newberne and Wilson 1970). No significant changes in hemoglobin, erythrocytes, leukocytes, or differential leukocyte counts were observed in Wistar rats exposed to pyrogenic a-silica at dietary doses up to 1,000 mg/kg/day for 5 weeks, TWA doses of 7,500 mg/kg/day for 8 weeks, or 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). In F344 rats, no biologically relevant changes in hemoglobin, hematocrit, erythrocytes, leukocytes, or differential leukocyte counts were observed following exposure to a-silica gel at dietary doses up to 2,410 mg/kg/day for 26 weeks, 2,220 mg/kg/day for 52 weeks, or 2,020 mg/kg/day for 103 weeks, compared with controls (Takizawa et al. 1988). Similarly, no biologically relevant changes in hemoglobin, hematocrit, erythrocytes, leukocytes, or differential leukocyte counts were observed in B6C3F1 mice exposed to a-silica gel at dietary doses up to 9,810 mg/kg/day for 26 weeks, 7,560 mg/kg/day for 52 weeks, or 6,010 mg/kg/day for 93 weeks, compared with controls (Takizawa et al. 1988).

No significant changes in bone marrow histology were observed in Wistar rats exposed to pyrogenic a-silica at dietary doses of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994).

2.8 MUSCULOSKELETAL

Crystalline Silica, Oral. No studies evaluating musculoskeletal effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating musculoskeletal effects in humans following inhalation exposure to a-silica were identified. No treatment-related changes in skeletal muscle histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

Amorphous Silica, Oral. No studies evaluating musculoskeletal effects in humans or animals following oral exposure to a-silica were identified.

2.9 HEPATIC

Crystalline Silica, Oral. No studies evaluating hepatic effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating hepatic effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in liver clinical chemistry were observed in rats exposed to colloidal a-silica at concentrations up to 150 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks (Lee and Kelly 1992). No treatment-related changes in liver clinical chemistry, organ weight, or histology were observed in rats exposed to pyrogenic or precipitated a-silica at 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

Hepatocellular vacuolation was reported in monkeys exposed to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for 12 months (Schepers 1962). In another chronic study, no changes in liver clinical chemistry or histology were observed in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating hepatic effects in humans following oral exposure to a-silica were identified. Severe atrophy of the hepatic epithelium was observed in male and female Wistar rats following dietary exposure to pyrogenic a-silica TWA doses of 7,500 mg/kg/day for 8 weeks; incidence data were not provided (Lewinson et al. 1994). Daily concentrations were 2,000 mg/kg/day during weeks 0–2, 4,000 mg/kg/day during weeks 2–4, 8,000 mg/kg/day during weeks 4–6, and 16,000 mg/kg/day during weeks 6–8. Liver cells showed condensation of the cytoplasm, loss of basophilic structure, and hyperchromatic and contracted nuclei. These changes were seen sporadically in females (2/10) exposed to pyrogenic a-silica at dietary doses of 1,000 mg/kg/day for 5 weeks, but not males at 1,000 mg/kg/day or either sex at ≤500 mg/kg/day (Lewinson et al. 1994). In a 2-generation study, no exposure-related changes in liver weight or histology were observed in F0 or F1 adult Wistar rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day for approximately 18 weeks (Wolterbeek et al. 2015).

Similarly, no significant changes in liver weight or histology were observed in Wistar or F344 rats exposed to dietary a-silica (pyrogenic or gel) at doses up to 2,410 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994; Takizawa et al. 1988).

In B6C3F1 mice, a significant 16% decrease in liver weight was observed in females exposed to dietary a-silica gel at a dietary dose of 9,810 mg/kg/day; liver weights were not decreased in female mice at

3,780 mg/kg/day or male mice at doses up to 6,700 mg/kg/day (Takizawa et al. 1988). No treatment-related changes in liver histology were reported in male or female B6C3F1 mice exposed to a-silica gel for 26 weeks at dietary doses up to 6,700 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

A significant 14–15% decrease in liver weight was observed in female F344 female rats exposed to a-silica gel at dietary doses ≥980 mg/kg/day for 103 weeks; liver weights were not decreased in females at 480 mg/kg/day for 103 weeks, males at doses up to 910 mg/kg/day for 103 weeks, or males or females at doses up to 2,220 mg/kg/day for 52 weeks (Takizawa et al. 1988). No treatment-related histopathological lesions in the liver were observed in rats exposed to a-silica gel for 52 or 103 weeks at dietary doses up to 2,220 mg/kg/day (Takizawa et al. 1988). Similarly, no histopathological changes in the liver were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). In B6C3F1 mice, no significant changes in liver weight or histology were observed following exposure to a-silica gel at dietary doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

2.10 RENAL

Crystalline Silica, Inhalation.

Renal Effects Associated with Crystalline Silica Exposure. General information on renal effects associated with exposure to c-silica was taken from the following publications: Beckett et al. (1997); Ghahramani (2010); Goldsmith and Goldsmith (1993); Gomez-Puerta et al. (2013); IARC (1997); NIOSH (2002); Steenland (2005); and Steenland et al. (2002a).

"*Silicon nephropathy"* was first described in the mid-1970s in c-silica-exposed workers with overt silicosis, and was characterized by a wide-spectrum of renal pathologies, including acute and chronic renal nephritis/nephrosis, end-stage renal failure, and glomerulonephritis. During the 1980s, renal damage associated with autoimmune disease was described in c-silica-exposed workers in the absence of silicosis (e.g., ANCA-associated vasculitis; see Section 2.14 Immunological and Lymphoreticular Effects for more details). Based on these findings, there appears to be two types of c-silica-induced renal disease: (1) a direct toxic effect of excessive c-silica accumulation in the kidney, and (2) an indirect toxic effect secondary to autoimmune disease (see Section 3.21.2 Mechanisms of Toxicity for more details).

Subsequent to initial case reports of renal disease in c-silica-exposed workers, associations between exposure to c-silica and risk of renal disease have been examined in retrospective and cross-sectional studies (Birk et al. 2009; Boujemaa et al. 1994; Calvert et al. 1997, 2003; Cocco et al. 1994; El-Safty et al. 2003; Fenwick and Main 2000; Hotz et al. 1995; Ibrahim et al. 2011; Koskela et al. 1987b; McDonald et al. 2001, 2005; Millerick-May et al. 2015; Ng et al. 1992, 1993; Rapiti et al. 1999; Rosenman et al. 2000; Steenland and Brown 1995b; Steenland et al. 1990, 1992, 2001b, 2002a, 2002b; Vupputuri et al. 2012; Wyndham et al. 1986). In general, these studies have found increased risk of kidney disease and/or subclinical signs of renal dysfunction in workers exposed to c-silica, and a limited number of studies have found increasing risk in association with increasing cumulative exposure to c-silica. Most of these studies have estimated risk in terms of incidence or mortality in the cohort in comparison life table analysis of data from regional or national reference populations. Most studies did not evaluate the potential contribution of other work-related factors to renal disease, including exposure to other nephrotoxicants (e.g., metals), complications from lung disease or silicosis, or differential prevalence of other risk factors (e.g., diabetes, cardiovascular disease, smoking, etc.).

Renal Disease: Incidence and Exposure-Response Data. Studies examining the exposure-relationship between c-silica and incidence of renal disease are summarized in Table 2-10 (Calvert et al. 1997; Rapiti et al. 1999; Steenland et al. 2001b). Calvert et al. (1997) evaluated the exposure-response relationship for renal disease in male gold miners exposed to estimated mean cumulative c-silica dust levels of 0.39 mg/m^3-year. The overall incidence of end-stage renal disease in this study population was 0.46% (11/2,412 workers). The standardized incidence ratio (SIR) for nonsystemic end-stage renal disease (end-stage renal disease associated with glomerulonephritis or interstitial nephritis) was 4.22 (95% CI: 1.54, 9.18), suggesting a 4-fold greater risk for gold miners compared to the U.S. population. The SIR for all end-stage renal disease was 1.37 (95% CI: 0.68, 2.46). When stratified by exposure duration, the risk of nonsystemic end-stage renal disease was markedly increased (SIR: 7.70; 95% CI: 1.59, 22.48) for workers exposed for <10 years. When stratified by cumulative exposure, the risk of nonsystemic end-stage renal disease was increased for estimated cumulative exposures in the 0.22–<0.55 mg/m^3-year tertile (SIR: 11.05; 95% CI: 3.01, 28.03), but not for higher (≥0.55 mg/m^3-year) cumulative exposures. The SIR for all end-stage renal disease was 1.37 (95% CI: 0.68, 2.46). In a population of male ceramic workers, the incidence of end-stage renal disease was 0.21%, with a 3.12-fold (95% CI: 1.17, 6.98) elevated increased risk over the full estimated cumulative exposure range of 0.2–3.8 mg/m^3-year (Rapiti et al. 1999). However, exposure duration was not consistently associated with increased risk of renal

Table 2-10. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Calvert et al. 1997	Study design: retrospective cohort study Industry: gold miners Location: South Dakota, United States	Cohort: 2,412 male miners employed for at least 1 year between 1940 and 1965, who were still alive on January 1, 1977 Adjustments: see statistical analysis Statistical analysis: SIR with U.S. population as the reference. Life-table analysis, which accounts for age, race, sex, and time and calendar intervals for the U.S. population	Mean cumulative c-silica dust exposure (mg/m^3-year): 0.39 Cumulative exposure (mg/m^3-year) tertiles for c-silica dust: - T1: <0.22 - T2: 0.22–<0.55 - T3: ≥0.55 Exposure duration tertiles (years): - T1: <5 - T2: 5–9.9 - T3: ≥10	The SIR for all cases of end-stage renal disease was not increased; however, the SIR for nonsystemic cases (caused by glomerulo-nephritis or interstitial nephritis) was increased. Total cases - Number of cases: 11 - SIR (95% CI): 1.37 (0.68, 2.46) Nonsystemic cases - Number of cases: 6 - SIR (95% CI): 4.22 (1.54, 9.18) - SIR (95% CI) [number of cases] by exposure tertile: T1: 1.27 (0.03, 7.08) [1] T2: 11.05 (3.01, 28.30) [4] T3: 3.68 (0.09, 20.52) [1] - SIR (95% CI) [number of cases] by duration tertile: T1: 2.59 (0.31, 9.36) [2] T2: 3.86 (0.10, 21.50) [1] T3: 7.70 (1.59, 22.48) [3]

Table 2-10. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Rapiti et al. 1999	Study design: prospective cohort study Industry: ceramic workers Location: Lazio, Italy	Cohort: 2,820 male ceramic workers followed from 1974 to 1991 in a health surveillance program with annual medical examination Adjustments: see statistical analysis Statistical analysis: SIR with regional disease registry data as the reference. Life-table analysis, which accounts for age, race, sex, and time and calendar intervals for the U.S. population	Range of cumulative c-silica dust exposure in end-stage renal cases (mg/m^3-year): 0.2–3.8	The SIR for incidence of end-stage renal disease was elevated. - Number of cases: 6 - SIR (95% CI): 3.21 (1.17, 6.98) - SIR (95% CI) [number of cases] by latency since first exposure: <10 years: 25.0 (0.65, 139) [1] 10–19 years: 4.65 (1.26, 11.9) [4] 20–29 years: N/A [0] ≥30 years: 2.85 (0.07, 15.9) [1]

Table 2-10. Renal Disease Morbidity in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
Steenland 2005; Steenland et al. 2001b	Study design: historical cohort study Industry: industrial sand workers Location: United States	Cohort: 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure Adjustments: age, race, sex, calendar time Statistical analysis: SMR with U.S. population as the reference; standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m^3-year): 0.13[a] Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SIR (95% CI)) for end-stage renal disease was increased, but did not show an exposure-related trend over exposure quartiles. - Number of cases: 23 - SIR for whole cohort: 1.97 (1.25, 2.96) - SRR by quartile (number of cases) Q1: 1.00 (2) (referent) Q2: 3.09 (5) Q3: 5.22 (6) Q4: 7.79 (5) - Slope [change in rate per 1 mg/m^3-year increase (95% CI)]: 0.00043 (0.00027, 0.00062) The SIR (95% CI) for glomerular disease was increased: - Number of cases: 7 - SIR: 3.85 (1.55, 7.93) Comparative lifetime risks (age 75) for end-stage kidney disease incidence after 45 years of exposure: - 0.1 mg/m^3 exposure: 5.1% (95% CI: 3.3, 7.3) - 0.01 mg/m^3 exposure: 0.5% (95% CI: 0.3, 0.8) - Background risk: 2%

[a]Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; N/A = not applicable; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SRR = standardized rate ratio

disease. The SIR for end-stage renal disease was increased in a population of industrial sand workers (SIR: 1.97; 95% CI: 1.25, 2.96); however, no trend was observed with increasing exposure (Steenland et al. 2001b).

The remaining exposure-response data for renal disease come from the review of death certificates that list the presence of renal disease at death, whether or not it was the underlying cause of death (see discussion below, "Renal Disease Mortality: Exposure-Response Data").

Results of a pooled-analysis of three cohorts provide stronger evidence for increased risk of renal disease in workers in association with estimated exposures to c-silica. Steenland et al. (2002a) analyzed mortality findings from three cohorts in a pooled-cohort analysis of industrial sand workers (Steenland et al. 2001b), gold miners (Steenland and Brown 1995b), and granite workers (Costello and Graham 1988) (Table 2-11). Based on SMRs for the entire cohort (estimated exposure range: 0.15–≥1.67 mg/m^3-year), excess mortality due to renal disease was observed (SMR: 1.41; 95% CI: 1.05, 1.47), with a monotonic increase over exposure quartiles (linear trend test; p=0.0007). Based on ORs, an increased risk for renal disease as the underlying cause of death was observed in the highest quartile of ≥1.67 mg/m^3-year (OR: 3.93; 95% CI: 1.31, 11.76), but not in quartiles <1.67 mg/m^3-year. Although the log-trend value across quartiles for renal disease as the underlining cause of death was statistically significant (p=0.03), the p-value for linear trend was not significant (p=0.21). For the presence of renal disease at death (multiple cause), a positive linear trend was observed for SMRs across the exposure range (linear trend test; p<0.000001). Based on ORs across quartiles, the presence of renal disease at death was increased in the 0.55–<1.67 mg/m^3-year quartile (OR: 1.77; 95% CI: 1.10, 2.86) and the ≥1.67 mg/m^3-year quartile (OR: 2.86; 95% CI: 1.73, 4.72); positive trends were observed by both linear (p=0.004) and log (p=0.0002) trend analyses. Results of this study suggest that exposure to c-silica is associated with increased risk of death from renal disease. Based on the pooled data, comparative lifetime risks (age 75) for death from chronic end-stage renal disease after 45 years of exposure were estimated to be 0.8% (95% CI: 0.1, 3.4%) at 0.01 mg/m^3 and 1.8% (95% CI: 0.8, 9.7%) at 0.1 mg/m^3 (background risk: 0.3%) (Steenland 2005; Steenland et al. 2002a).

Mohner et al. (2017) conducted a meta-analysis of 23 occupational cohort studies and 4 case-control studies of chronic kidney disease among workers in various industries where silica exposures occur (e.g., granite, metal and coal mining, sand, porcelain, pottery, diatomaceous earth). Outcomes across studies were mixed. Outcomes of studies of workers identified as having silicosis were mixed, although the study group mean SMR was 1.28 (95% confidence limit [CL]: 1.01, 1.62). Outcomes of studies of

Table 2-11. Exposure-Response Analysis for Renal Disease Mortality in a Pooled Cohort of 13,382 Workers

Cohorts	Methods	Outcomes for pooled cohort
Pooled cohort: - 13,382 workers exposed to c-silica from 3 cohorts (12,783 with exposure data) - Total deaths with renal disease listed as underlying cause: 51 (50 deaths with exposure data) - Total deaths with renal disease listed as underlying or contributory cause: 204 (193 deaths with exposure data) - Mean exposure duration (years): 13.6[a] - Mean cumulative exposure (mg/m^3-year): 1.2[a] Three cohorts: Steenland et al. 2001b - Industrial sand workers: 4,027 - Location: United States - Deaths due to renal disease (underlying cause): 13 - Deaths due to multiple causes (renal disease listed on death certificate): 52 - Mean exposure duration (years): 3.7[b] - Mean cumulative exposure (mg/m^3-year): 0.13[b] Steenland and Brown 1995b - Gold miners: 3,328 - Location: United States - Deaths due to renal disease (underlying cause): 13 - Deaths due to multiple causes (renal disease listed on death certificate): 42 - Mean exposure duration (years): 5.4[c] - Mean cumulative exposure (mg/m^3-year): 0.23[c] Costello and Graham 1988 - Granite workers: 5,408 - Location: United States - Deaths due to renal disease: Not reported by study authors; determined by Steenland et al. (2002a) via review of death certificates (calculated number not reported) - Mean exposure duration (years): 18.0[d]	Cause of death: renal disease (acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, renal sclerosis, and nephritis/nephropathy) Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: <0.15 (referent) Q2: 0.15–<0.55 Q3: 0.55–<1.67 Q4: ≥1.67 Adjustments: age, race, sex, calendar time Statistical analysis: SMR with U.S. population as the reference; conventional life table analyses	The SMR for renal disease as the underlying cause for death was significantly increased in an exposure-related manner: - Number of deaths: 50 - SMR for whole cohort (95% CI): 1.41 (1.05, 1.85) - SMR by quartile (number of deaths) Q1: 0.55 (4) Q2: 0.94 (8) Q3: 1.17 (10) Q4: 2.23 (28) p-value for trend = 0.0007 Deaths due to renal disease increased with increasing cumulative exposure. OR (95% CI) by quartile of cumulative exposure: - Q1: 1.00 - Q2: 1.88 (0.62, 5.70) - Q3: 1.96 (0.66, 5.84) - Q4: 3.93 (1.31, 11.76) p-value (linear) = 0.21 p-value (log) = 0.03 The SMR for presence of renal disease at death was significantly elevated in an exposure-related manner: - Number of cases present at death: 193 - SMR for whole cohort (95% CI): 1.28 (1.10, 1.47). - SMR by quartile (number of cases) Q1: 0.93 (32) Q2: 0.93 (36) Q3: 1.51 (52) Q4: 1.60 (62)

Table 2-11. Exposure-Response Analysis for Renal Disease Mortality in a Pooled Cohort of 13,382 Workers

Cohorts	Methods	Outcomes for pooled cohort
- Mean cumulative exposure (mg/m^3-year): 0.71[d]		p-value for trend <0.000001 The presence of renal disease at death increased with increasing cumulative exposure. OR (95% CI) by quartile of cumulative exposure: - Q1: 1.00 - Q2: 1.24 (0.77, 2.01) - Q3: 1.77 (1.10, 2.85) - Q4: 2.86 (1.73, 4.72) p-value (linear) = 0.004 p-value (log) = 0.0002 Comparative lifetime risks at age 75 (95% CI) for end-stage kidney disease incidence after 45 years of exposure: - 0.1 mg/m^3 exposure: 1.8% (0.8, 9.7%) - 0.01 mg/m^3 exposure: 0.8% (0.1, 3.4) - Background risk: 0.3%

[a]Mean exposure durations and cumulative exposures were estimated by Steenland et al. (2002a) (not reported in original publication), based on job-exposure matrices data provided by the original investigators for each cohort. Estimated values for each cohort were not reported by Steenland et al. (2002a).
[b]Exposure estimates reported here were calculated by Mannetje et al. (2002a, 2002b) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b).
[c]Exposure estimates reported here were calculated by Mannetje et al. (2002a, 2002b) for Steenland and Brown (1995a, 1995b).
[d]Exposure estimates reported here were calculated by Mannetje et al. (2002a, 2002b) for Costello and Graham (1988).

CI = confidence interval; OR = odds ratio; SMR = standardized mortality ratio

Sources: Steenland et al. (2002a); Steenland (2005)

industrial cohorts were also mixed. The group mean was 1.52 (95% CL: 1.16, 1.98). Group means for the various industries were as follows: pottery (n=3) 2.15 (95% CL: 1.13, 4.08); gold mining (n=2) 1.51 (95% CL: 1.07, 2.12); coal and iron ore (n=2) 0.99 (95% CL: 0.78, 1.25); and sand and granite (n=5) 1.59 (95% CL: 0.91, 1.78). Mohner et al. (2017) concluded that the meta-analysis did not provide clear evidence of dose-response relationships for renal disease.

In addition to the studies discussed above, other studies reported statistically significant increased incidence, SIRs, or ORs for renal disease in c-silica-exposed workers, but did not report quantitative cumulative exposure estimates or exposure-response data (Fenwick and Main 2000; Steenland et al. 1990, 1992; Vupputuri et al. 2012). However, SIRs were not statistically significant for increased end-stage renal disease in a cohort of individuals diagnosed with silicosis from a silicosis registry (Steenland et al. 2002b) or for chronic pyelonephritis in a cohort of male granite workers (Koskela et al. 1987b).

Impaired Renal Function. Several cross-sectional studies provide evidence that occupational exposure to c-silica can lead to subclinical signs of renal dysfunction; however, exposure levels were not reported in these studies (Boujemaa et al. 1994; El-Safty et al. 2003; Hotz et al.1995; Ibrahim et al. 2011; Millerick-May et al. 2015; Ng et al. 1992, 1993; Rosenman et al. 2000). Statistically significant ($p<0.05$) alterations observed in exposed workers from various industries (e.g., granite quarry workers, ceramic and glass workers, and miners), compared with unexposed or low-exposed referents, include increased urinary excretion of albumin, transferrin, α-1-microglobulin (AMG), and retinol-binding protein, elevated serum creatinine levels, and/or altered urinary β-N-acetyl-glucosaminidase (NAG) activity (Boujemaa et al. 1994; El-Safty et al. 2003; Hotz et al. 1995; Ibrahim et al. 2011; Ng et al. 1992, 1993; Rosenman et al. 2000). These effects have been observed in exposed workers with silicosis (Boujemaa et al. 1994; El-Safty et al. 2003; Ng et al. 1992; Rosenman et al. 2000) as well as in exposed workers without silicosis (El-Safty et al. 2003; Hotz et al. 1995; Ibrahim et al. 2011; Ng et al. 1992;). However, two studies reported a lack of correlation between severity of silicosis and the measures of renal function listed above (Boujemaa et al. 1994; Rosenman et al. 2000). Results of these studies suggest that renal damage may occur prior to, and independently of, the development of silicosis.

Renal Disease Mortality: Exposure-Response Data. Several studies have evaluated risk of death from renal disease in c-silica-exposed workers; see study details in Table 2-12 (McDonald et al. 2005; Steenland and Brown 1995b; Steenland et al. 2001b). Steenland et al. (2001b) reported a 2.22-fold (95% CI: 1.06, 4.08) increase in the number of deaths from chronic kidney disease in industrial sand workers exposed to a mean cumulative exposure of 0.13 mg/m^3-year (exposure levels estimated by Mannetje et al.

Table 2-12. Renal Disease Mortality in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
McDonald et al. 2005	Study design: historical cohort study with nested case-referent analysis Industry: industrial sand workers Location: United States (five states)[a]	Cohort: 2,452 male workers employed in eight plants for at least 3 years, working for ≥1 month during 1940–1979, with follow-up through 2000 Cases: 18 individuals that died from renal disease Referents: two referents were identified for each case from cohort members employed at the same plant, born within 5 years (3 years if possible) of the case, first hired within 5 years (3 years if possible) of the case, and who survived the case Adjustments: case-referent analysis was adjusted for matching Statistical analysis: Poisson regression model (SMR); conditional multiple logistic regression (case-referent)	Cumulative exposure (mg/m^3-year) for respirable c-silica: - ≤1 (referent) - 1–≤1.5 - 1.5–≤ 5 - >5	The SMR for all deaths due to nephritis/ nephrosis showed a statistically significant increase: - Number of deaths: 18 - SMR: 2.8 ($p<0.001$) Deaths due to nephritis/nephrosis did not show statistically significant increases with cumulative exposure. Adjusted ORs (lagged by 0 and 15 years to accommodate disease latency): 0-year lag - ≤ 1 (referent): 1.00 - >1–≤1.5: 0.61 - >1.5–≤5: 0.16 - >5: 0.16 15-year lag - ≤0.3 (referent): 1.00 - >0.3–≤1.2: 0.79 - >1.2–≤4: 0.19 - >4: 0.19

Table 2-12. Renal Disease Mortality in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Steenland and Brown 1995b	Study design: historical cohort study Industry: gold miners Location: South Dakota, United States	Cohort: 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years) Adjustments: see statistical analysis Statistical analysis: life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with χ^2 tests	Median cumulative exposure (mg/m^3-year): 0.23[b]	The SMRs for kidney disease were not elevated. Acute kidney disease: - Number of deaths: 2 - SMR (95% CI): 1.19 (0.14, 4.29) Chronic kidney disease: - Number of deaths: 11 - SMR (95% CI): 1.25 (0.62, 2.23) The SMRs for chronic renal disease showed statistically significant increases with increased cumulative dust exposure (dust-days)[c]: - <8,000: 0.40 - 8,000–<32,000: 0.34 - 32,000–<48,000: 1.26 - ≥48,000: 2.77 χ^2=7.62 *p*≤0.05

Table 2-12. Renal Disease Mortality in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Steenland et al. 2001b	Study design: historical cohort study Industry: industrial sand workers Location: United States (11 states)	Cohort: 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 with adequate work histories to estimate exposure Adjustments: age, race, sex, calendar time Statistical analysis: standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m^3-year): 0.13[d] Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SMRs for chronic, but not acute, kidney disease were elevated. Acute kidney disease: - Number of deaths: 3 - SMR (95% CI): 3.37 (0.70, 9.86) - A positive trend over exposure quartiles: Slope [change in rate per 1 mg/m^3-year increase (95% CI)]: 0.00007 (0.00003, 0.00012) Chronic kidney disease: - Number of deaths: 10 - SMR (95% CI): 2.22 (1.06, 4.08) - No trend over exposure quartiles: slope [change in rate per 1 mg/m^3-year increase (95% CI)]: 0.00043 (0.00027, 0.00062)

[a]States were identified in the companion study (McDonald et al. 2001).
[b]Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication), based on data provided by the original investigators.
[c]One dust-day is 1 day with an exposure of 1 mppcf dust; 10 mppcf of respirable dust = 0.1 mg c-silica/m^3.
[d]Exposures were not reported in the original publication; however, they were estimated by Mannetje et al. (2002a, 2002b) for Steenland and Sanderson (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; mppcf = millions of particles per cubic foot of air; OR = odds ratio; SMR = standardized mortality ratio

2002b). A positive trend was observed for acute renal disease (slope [change in disease rate per 1 mg/m^3-year increase in exposure]: 0.00007; 95% CI: 0.00003, 0.00012), but not chronic renal disease. The risk of death from acute kidney disease was not elevated in this cohort (Steenland et al. 2001b). Similarly, a study of industrial sand workers reported a significant 2.8-fold increase ($p<0.001$) in deaths due to nephritis/nephrosis (McDonald et al. 2005). In gold miners exposed to an estimated mean cumulative exposure of 11.37 mg/m^3-year, there was no significant increase in the SMR for death due to either acute or chronic kidney disease; however, the SMRs for death due to chronic renal disease showed statistically significant ($p\leq0.05$) associations with increased cumulative dust exposure (Steenland and Brown 1995b; exposure levels estimated by Mannetje et al. 2002b). Findings from these studies are not consistent and are difficult to compare due to different study designs, follow-up periods, and categorization of renal disease at death. Several other studies without quantitative exposure data have evaluated SMRs due to nonmalignant renal diseases. Increased SMRs and/or mortality odds ratios were reported in industrial sand workers, and gold, lead, and zinc miners (Cocco et al. 1994; McDonald et al. 2001; Wyndham et al. 1986). However, SMRs were not increased in pottery workers (Birk et al. 2009), granite cutters (Steenland et al. 1992), or workers from various industries categorized as having high or very-high c-silica exposure (Calvert et al. 2003).

Steenland et al. (2002a) evaluated mortality due to renal disease in a pooled analysis of 13,382 workers from three cohorts of industrial sand workers (Steenland et al. 2001b), gold miners (Steenland and Brown 1995b), and granite workers (Costello and Graham 1988); study details are summarized in Table 2-11. SMRs were estimated based on life table analysis of data from the U.S. population. For the entire cohort (exposure range: 0.15–≥1.67 mg/m^3-year), increased risks were observed for renal disease as the underlying cause of death (SMR: 1.41; 95% CI: 1.05, 1.85). Examined by exposure quartiles, the risk of death due to renal disease was increased in the highest estimated exposure quartile (≥1.67 mg/m^3-year; OR: 3.93; 95% CI: 1.31, 11.76). Over all estimated exposure quartiles, a positive exposure trend was observed for renal disease as the underlying cause of death ($p=0.0007$).

Crystalline Silica, Oral. The relationship between Balkan nephropathy (BN; an endemic chronic kidney disease of the Balkan Peninsula) and well water chemical composition and characteristics was evaluated in 366 inhabitants of Petka, Serbia, a village affected by BN, from January 1974 to December 1985 (Radovanovic et al. 1991). Silicon dioxide and nitrate content of the 85 wells used by study subjects were measured during June and August 1974. Wells used by each study subject for at least 1 year during the 12-year period, as well as during the 30 preceding years, were identified, and the data were analyzed as "person/wells". A total of 28 individuals using 24 wells were diagnosed with BN. Using a multiple

logistic regression model, silicon dioxide levels were significantly positively correlated with developing BN (regression coefficient ± standard error: 0.0611±0.023; standardized regression coefficient=2.63; p=0.008). The mean (± standard deviation) well water silicon dioxide levels in the BN-affected group (33.79±6.09 mg/L) was 11% greater than the mean (± standard deviation) silicon dioxide levels in the BN-spared group (30.52±8.02 mg/L). Additionally, well altitude was significantly inversely correlated with developing BN (regression coefficient ± standard deviation: -0.4075±0.016; standardized regression coefficient: -2.97; p=0.001). While significant findings suggest a correlation between silicon dioxide content in well water and BN, Radovanovic et al. (1991) suggested that the magnitude of change is too small to be a biologically plausible effect mechanism. Additionally, silicon dioxide content of well water only explained 6.9% of the total variability. The study authors proposed that it is more likely that the silicon dioxide content in well water is correlated with the disease, rather than the underlying cause of the BN. Although the etiology of BN remains unknown, several possible causes have been proposed including viral, environmental, and genetic risk factors. Exposure to trace elements, including silica, are included in the list of potential risk factors, but current research has been more focused on mycotoxins, phytotoxins (particularly aristolochic acid), and genetic predisposition (reviewed by Schiller et al. 2008; Voice et al. 2006). Additionally, lower silica content (unspecified form, assumed to be c-silica) has been reported in wells from BN-endemic villages, compared to higher silica content in well water of the control villages (reviewed by Voice et al. 2006).

Focal nephritis in the distal tubule and collecting duct was observed in two of six male guinea pigs exposed to 51 mg c-silica/kg/day as crushed quartz in drinking water for 5 days/week for 4 months; no kidney lesions were observed in the six control animals (Dobbie and Smith 1982). Observed renal lesions were most evident in the subcapsular and corticomedullary regions, and included dilation, cystic changes, chronic inflammatory infiltrate, increased collagen fibers, and proteinaceous material. No renal lesions were observed in animals similarly exposed to 51 mg c-silica/kg/day as crushed granite (Dobbie and Smith 1982). This study indicates that the form of c-silica is important with regard to the degree and extent of renal toxicity.

No significant changes in glomerular filtration rate or urine output were observed in 3-month-old albino rats exposed to 50 mg c-silica/kg-day as sodium metasilicate in drinking water for 8 days, compared with controls; the baseline c-silica content in drinking water was 267 µg/L (Öner et al. 2005, 2006). After exposure, rats were sacrificed and renal cortical slices were obtained for culture. Total ammonia levels, ammonia secretion rate, and gamma-glutamyl transpeptidase (γ-GT) were significantly ($p<0.05$) elevated and total glutamine content was significantly ($p<0.05$) decreased in renal slices from exposed rats,

compared with controls. Ammoniagenesis associated with c-silica exposure could potentially lead to altered function of renal proximal tubule cells. The toxicological significance of these findings is not established.

Amorphous Silica, Inhalation. No studies evaluating renal effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in kidney clinical chemistry were observed in rats exposed to colloidal a-silica at concentrations up to 150 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks (Lee and Kelly 1992). No treatment-related changes in kidney clinical chemistry, organ weight, or histology were observed in rats exposed to pyrogenic or precipitated a-silica at 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

Renal congestion and cloudy swelling of the convoluted tubules were observed in monkeys exposed to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for 12 months (Schepers 1962). These findings may be due to general compound toxicity rather than specific renal pathology. In another chronic study, no changes in renal clinical chemistry or histology were observed in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating renal effects in humans following oral exposure to a-silica were identified.

No changes in renal clinical chemistry, weight, or histology were observed in Beagle dogs exposed to silicon dioxide (unspecified) at dietary doses of 800 mg/kg/day for 4 weeks (Newberne and Wilson 1970).

No adverse kidney effects have been reported in rats following intermediate-duration oral exposure to a-silica. No changes in kidney clinical chemistry, weight, or histology were observed in CD rats exposed to silicon dioxide (unspecified) at dietary doses of 800 mg/kg/day for 4 weeks (Newberne and Wilson 1970).

No exposure-related changes in kidney weight and/or histology were observed in Wistar rats exposed to pyrogenic a-silica at dietary doses up to 1,000 mg/kg/day for 5 weeks, pyrogenic a-silica at TWA doses of 7,500 mg/kg/day for 8 weeks, precipitated a-silica at gavage doses up to 1,000 mg/kg/day for

approximately 18 weeks, or dietary a-silica (pyrogenic or gel) at doses up to 2,410 mg/kg/day for 6 months (Lewinson et al. 1994; Wolterbeek et al. 2015).

Similarly, no significant changes in kidney weight or histology were observed in F344 rats exposed to dietary a-silica (pyrogenic or gel) at doses up to 2,410 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994).

In B6C3F1 mice, a significant 15–22% decrease in kidney weight was observed in females exposed to a-silica gel at dietary doses ≥3,780 mg/kg/day; kidney weights were not decreased in female mice at 2,070 mg/kg/day or male B6C3F1 mice at doses up to 6,700 mg/kg/day (Takizawa et al. 1988). No treatment-related changes in kidney histology were reported in male or female B6C3F1 mice exposed to a-silica gel for 26 weeks at dietary doses up to 6,700 or 9,810 mg/kg/day, respectively (Takizawa et al. 1988).

No renal effects have been associated with chronic oral exposure to a-silica. No changes in kidney histology were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant changes in kidney weight or histology were observed in F344 rats exposed to a-silica gel at dietary doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant changes in kidney weight or histology were observed following exposure to a-silica gel at dietary doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

2.11 DERMAL

Crystalline Silica, Oral. No studies evaluating dermal effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating dermal effects in humans following inhalation exposure to a-silica were identified. No treatment-related changes in skin histology were observed rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991) or in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating dermal effects in humans or animals following oral exposure to a-silica were identified.

2.12 OCULAR

Crystalline Silica, Oral. No studies evaluating ocular effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating ocular effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in eye histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

Amorphous Silica, Oral. No studies evaluating ocular effects in humans or animals following oral exposure to a-silica were identified.

2.13 ENDOCRINE

Crystalline Silica, Oral. No studies evaluating endocrine effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating endocrine effects in humans following inhalation exposure to a-silica were identified. No treatment-related changes in adrenal weight or endocrine organ histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No changes in adrenal, thyroid, or pancreas histology were observed in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981). No changes in adrenal, thyroid, parathyroid, or pancreas histology were observed in monkeys following exposure to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for 12 months (Schepers 1962).

Amorphous Silica, Oral. No studies evaluating endocrine effects in humans following oral exposure to a-silica were identified. In a 2-generation study in Wistar rats, no exposure-related changes were observed in adrenal, thyroid, pituitary gland, ovary, or testes weights or histology in F0 or F1 parental animals following exposure to gavage doses up to 1,000 mg/kg/day for approximately 18 weeks (Wolterbeek et al. 2015). In an intermediate-duration study, no significant changes in adrenal, pituitary, ovary, or testes weights or histology were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the thyroid (thyroid weights not recorded). In a chronic study, no changes in testes or ovary histology were observed in male and female Wistar rats exposed to pyrogenic a-silica at a dietary dose of 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

2.14 IMMUNOLOGICAL

Crystalline Silica, Inhalation.

Autoimmune Disorders Associated with Crystalline Silica Exposure: Pathologic Features and Clinical Presentation. Unless otherwise noted, information in the following section is from the following reviews and meta-analyses: Beckett et al. (1997); Deane and El-Gabalawy (2014); Demoruelle et al. (2014); Ghahramani (2010); Gibelin et al. (2011); Gomez-Puerta et al. (2013); Hinchcliff and Varga (2008); Hogan et al. (2001); Iannello et al. (2002); IARC (1997); Lee et al. (2012, 2014); Maeda et al. (2010); Manson and Rahman (2006); McCormic et al. (2010); NIOSH (2002); Otsuki et al. (2007); Parks et al. (1999); Steenland and Goldsmith (1995); Stratta et al. (2001a); Thomeer et al. (2005); and Wu and Schiff (2004).

No immune disorders are uniquely associated with exposure to c-silica. However, a link between c-silica exposure and autoimmune disease has been proposed since the late 1950s. Since the late 1960s, 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; Shtraichman et al. 2015; 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). Findings of these studies have been mixed with some finding associations with estimated exposures to c-silica and others finding no association. There is some evidence that observed autoimmunity may be a complication of silicosis, but autoimmunity may occur subsequent to direct toxic effects of excessive c-silica accumulation in the lymphatic system (see Section 2.20.2 Mechanisms of Toxicity for more details). It is important to note that mortality studies underestimate the prevalence of nonlethal disorders, and occupational cohort studies are often too small to accurately estimate the risk of rare diseases, such as autoimmune disorders. Thus, quantitative risk estimates should be interpreted with caution. Brief descriptions of autoimmune diseases potentially associated with c-silica exposure are listed below.

Systemic sclerosis (SSc). SSc is a multisystem disease of unknown etiology, but hypothesized causes include genetic, autoimmune, and environmental factors. Certain SSc subtypes have been associated with specific autoantibodies, including antinuclear antibody, anticentromere antibody, and antitopoisomerase-1 antibody. The disease is characterized by tissue thickening and fibrosis throughout the body. The most common clinical manifestations of the disease are scleroderma (hardening of the skin) and Raynaud phenomenon (recurrent vasospasm typically in the distal extremities). Fibrosis can also cause various types of internal organ dysfunction, which can be life threatening, such as decreased pulmonary function and pulmonary arterial hypertension. Other clinical signs include musculoskeletal complaints (arthralgia, myalgia, contractures), gastrointestinal complaints (reflux, intestinal dysmotility), and abnormal cardiac conduction. The estimated prevalence of SSc in the United States is 0.0009–0.03% (Hemlick et al. 2008; Hinchcliff and Varga 2008; Makol et al. 2011; Rosenman et al. 1999). Reported incidence of SSc in retrospective cohorts of c-silica-exposed workers ranges from 0.02 to 17% (Brown et al. 1997; Calvert et al. 2003; Gold et al. 2007; Makol et al. 2011; Rosenman et al. 1999; Walsh 1999).

Rheumatoid arthritis (RA). RA is an autoimmune disease characterized by systemic inflammation, with the hallmark of the disease being joint inflammation (synovitis) leading to progressive arthritic symptoms. Other tissues with inflammation associated with RA include the oral mucosa, pulmonary, and gastrointestinal tissues. RA is associated with specific autoantibodies, including rheumatoid factor and anti-citrullinated peptide antibody (ACPA). The etiology is unknown, but multiple genetic, epigenetic, and environmental risk factors have been proposed. The estimated prevalence of RA in the general U.S. population is 0.6–1.85%; in older adults (≥60 years of age), the estimated prevalence increases to 2.00–

2.34% (Hemlick et al. 2008; Makol et al. 2011; Rasch et al. 2003; Rosenman et al. 1999). Reported incidences of RA in cohorts of workers exposed to c-silica range from 0.4 to 5.2% (Brown et al. 1997; Klockars et al. 1987; Koskela et al. 1987b; Makol et al. 2011; Rosenman and Zhu 1995; Rosenman et al. 1999; Steenland et al. 2001b; Turner and Cherry 2000).

Systemic lupus erythematosus (SLE). SLE is an autoimmune disease that causes systemic inflammation. It is characterized by the presence of the antinuclear autoantibody. The etiology is unknown, but multiple genetic, epigenetic, and environmental risk factors have been proposed. Since it is a multi-system disease, clinical presentation often varies between patients. Common symptoms include a classic "malar" rash (fixed erythema over the malar eminences, tending to spare the nasolabial folds), a discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological (psychological) disorder, hematological disorder, and/or general symptoms of fatigue, weight loss, and fever. The estimated prevalence of SLE in the general U.S. population is 0.02–0.05% (Hemlick et al. 2008; Rosenman et al. 1999; Ward 2004). Estimates vary based on gender and race, with higher estimates for women (0.1% for white and Hispanic women and 0.4% for black women) compared with men (0.01 for white men and 0.05% for black men) (Hemlick et al. 2008; Makol et al. 2011; Ward 2004). Reported incidence of SLE in cohorts of c-silica-exposed workers ranges from 0.2 to 0.9% (Conrad et al. 1996; Makol et al. 2011; Rosenman et al. 1999).

ANCA-associated vasculitis (AAV). Vasculitides associated with serum positivity for ANCA are autoimmune disorders that affect blood vessels systemically. The most commonly associated diseases include granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS). These diseases are clinically associated with lung involvement, including diffuse alveolar hemorrhage (which can be lethal), parenchymal nodules and masses (in GPA), asthma and eosinophilic pneumonia (in CSS), or interstitial lung disease (in MPA). These diseases are often associated with renal damage (glomerulonephritis) as well, including focal glomerular necrosis and crescent formation. The estimated prevalences of GPA and vasculitis (not specified) in the United States are 0.003 and 0.03%, respectively (Gibelin et al. 2011; Makol et al. 2011). Prevalence of AAV in c-silica-exposed workers who were diagnosed with silicosis ranged from 0.8 to 2.23% (Makol et al. 2011).

Sarcoidosis. Sarcoidosis is a systemic granulomatous disease of unknown etiology, but hypothesized causes include genetic, autoimmune, and environmental factors. It is proposed that genetically susceptible individuals exposed to unknown environmental triggers may develop an exaggerated

inflammatory immune response. Sarcoidosis predominantly affects the lungs, although granulomas can also occur in skin, eyes, heart, liver, spleen, salivary glands, muscles, bones, kidneys, and central nervous system. It is characterized by noncaseating epithelioid granulomas that cannot be attributed to other granulomatous diseases. Patients with sarcoidosis often present with generalized symptoms (fever, fatigue, weight loss, malaise, myalgia, lymphadenopathy) as well as symptoms specific to affected organs (e.g., skin lesions, vision impairment, coughing, reduced lung function, arrhythmias, neuropathy, renal dysfunction). The estimated prevalence of sarcoidosis in the United States is 0.005–0.3% (Thomeer et al. 2005). Prevalence or incidence of sarcoidosis in c-silica-exposed workers has not been reported.

Autoimmune Disease: Incidence and Exposure-Response Data.

Systemic sclerosis/scleroderma (SSc). Two studies providing exposure data have evaluated the risk of SSc in c-silica-exposed workers (Steenland and Brown 1995b; Steenland et al. 2001b); however, these studies are of limited usefulness based on methods of analysis (e.g., grouping SSc with related disorders). Study details are provided in Table 2-13. In gold miners exposed to mean cumulative respirable c-silica levels of 11.37 mg/m^3-year, the incidences of "other musculoskeletal diseases" and "other diseases of the skin" at death (including SSc) were increased by 2.14-fold (95% CI: 1.03, 3.94) and 2.45-fold (95% CI: 1.17, 4.51), respectively (Steenland and Brown 1995b; exposure estimates calculated by Mannetje et al. 2002b). However, the incidence of SSc, specifically, was not reported or analyzed. In industrial sand workers exposed to lower cumulative levels of respirable c-silica (0.13 mg/m^3-year), the incidence of "other musculoskeletal diseases" (including SSc) was not increased (Steenland et al. 2001b; exposure estimates calculated by Mannetje et al. 2002b).

Numerous studies evaluated the potential association between SSc diagnosis and c-silica exposure; however, these studies did not report quantitative cumulative exposure estimates or exposure-response data. Several studies reported an elevated risk for SSc incidence or mortality in c-silica-exposed workers, often in individuals with silicosis (Brown et al. 1997; Cowie 1987; Diot et al. 2002; Englert et al. 2000; Marie et al. 2014; Rodnan et al. 1967; Walsh 1999), while others did not show associations with c-silica exposure (Bovenzi et al. 1995, 2004; Burns et al. 1996; Calvert et al. 2003; Gold et al. 2007; Lacey et al. 1997; Makol et al. 2011; Maitre et al. 2004; Rosenman et al. 1999; Silman and Jones 1992; Sluis-Cremer et al. 1985). However, a meta-analysis of 16 studies in c-silica-exposed workers (see Table 2-14 for study details) reported an increased combined estimator of relative risk (CERR) for SSc of 3.20 (95% CI: 1.89, 5.43) (McCormic et al. 2010). The risk was increased in males (CERR: 3.02; 95% CI: 1.24, 7.35), but not

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Rheumatoid arthritis (RA)				
Klockars et al. 1987; Koskela et al. 1987b	Study design: historical cohort study Industry: granite workers Location: Finland	Cohort: 1,026 male workers employed for at least 3 months between 1940 and 1971, with follow-up until 1981 (mean exposure duration: 12 years): - 170 quarry and drill workers - 119 saw workers - 160 cutters/dressers/ polishers - 452 general stone workers - 125 laborers Adjustments: none Statistical analysis: observed versus expected incidence: Poisson distribution model Incidence rates: Mantel-Haenszel χ^2 test	Geometric mean exposure to quartz particles <5 µm diameter (mg/m^3): - Drilling: 1.47 - Block surfacing: 0.82 - Other tasks: 0.12–1.44	Granite workers had a significantly higher incidence of free medicine grants for RA from national sickness insurance than the general population. Subjects receiving free medicines for RA: - Observed: 19 - Expected: 7.5 p<0.001 Granite workers had a significantly higher incidence of disability pensions for RA than the general population. Subjects receiving disability pensions for RA: - Observed: 10 - Expected: 1.6 p<0.001 Incidence rate/1,000 person years of awards of disability pensions for RA among granite workers and in general male population: - Granite workers: 1.69 - General population: 0.24 p<0.001 Note: The proportions of workers with RA in the various occupational categories (e.g., drillers, cutters, general workers, etc.) were comparable to the proportion in the total cohort.

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Steenland and Brown 1995b	Study design: historical cohort study Industry: gold miners Location: South Dakota, United States	Cohort: 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years) Adjustments: see statistical analysis Statistical analysis: life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with χ^2 tests	Median cumulative exposure (mg/m^3-year): 0.23[a]	The SMR for deaths that listed the presence of arthritis (including RA) was elevated: - Number of cases at death: 17 - SMR (95% CI): 2.19 (1.27, 3.50) Note: The number of RA cases was not specified.

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Steenland et al. 2001b	Study design: historical cohort study Industry: industrial sand workers Location: United States (11 different states)	Cohort: 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure Adjustments: age, race, sex, calendar time Statistical analysis: standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m^3-year): 0.13[b] Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SMR for deaths that listed the presence of arthritis (including RA) was elevated: - Number of cases at death: 23 - SMR (95% CI): 4.36 (2.76, 6.54) - SRR (number of deaths) by quartile (95% CI not reported): Q1: 1.00 (1) (referent) Q2: 1.73 (3) Q3: 3.73 (7) Q4: 6.91 (7) - A positive trend over exposure quartiles: Slope [change in rate per 1 mg/m^3-year increase (95% CI)]: 0.00018 (0.00017, 0.00019) Note: Of the death certificates mentioning arthritis, 12/23 specified RA. A SMR specific for RA was not reported.

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Turner and Cherry 2000	Study design: historical cohort study with nested case-referent analysis Industry: pottery, sandstone, and refractory material (aluminosilicate or c-silica) industries Location: United Kingdom	Cohort: 8,325 workers (6,353 men, 1,972 women) born in 1916–1945 and employed in pottery or related industries Cases: 58 workers (43 men, 15 women) who responded "yes" to the question on RA on the medical survey administered during routine occupational exam (administered every 2 years) Referents: 232 workers (172 men, 60 women); 4 referents matched to each case based on sex and as closely as possible to date of birth and date of first exposure to pottery Adjustments: smoking, employment in the coal mining industry, number of pregnancies Statistical analysis: conditional logistic regression	Mean cumulative exposure to respirable c-silica (mg/m^3-year): - Cases: 2.525 - Referents: 2.872 Mean (±SD) exposure concentration to respirable c-silica (mg/m^3): - Cases: 0.1329±0.0769 - Referents: 0.1329±0.0741	There was no increased risk of RA based on analysis of mean c-silica concentrations, cumulative exposure, or duration of employment. ORs (95% CI): Mean c-silica concentration/100 (µg/m^3): - Men: 0.79 (0.40, 1.57) - Women: 1.56 (0.36, 6.75) - Combined: 0.97 (0.56, 1.70) Cumulative exposure/1,000 (µg/m^3-year): - Men: 0.71 (0.52, 0.97) - Women: 1.13 (0.73, 1.73) - Combined: 0.80 (0.64, 1.02) Duration/1 (year): - Men: 0.29 (0.11, 0.76) - Women: 0.61 (0.18, 2.02) - Combined: 0.31 (0.16, 0.61) The prevalence of RA in this cohort (58/8325; 0.7%) is equal to the prevalence in the general United Kingdom population for individuals aged 45–64 years (0.7%).

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Vihlborg et al. 2017	Study design: retrospective cohort Industry: iron foundries Location: Sweden	Cohort: 2,187 male workers employed in 10 foundries, with employment for at least 1 year and beginning before 2005 Adjustments: none reported Statistical analysis: SIRs calculated using Poisson distribution of observed numbers	Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: 0.012–0.023 Q2: 0.024–0.035 Q3: 0.036–0.047 Q4: ≥0.048	The risk of seropositive RA was increased in the highest exposure quartile. SIR (95% CI): Q1: 1.20 (0.15, 4.32) Q2: 0.43 (0.01, 2.37) Q3: 1.86 (0.60, 4.33) Q4: 2.58 (1.24, 4.76)
Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE)				
Conrad et al. 1996	Study design: historical cohort study Industry: uranium miners Location: Germany	Cohort: 15,000 “heavily-exposed” workers with silicosis Adjustments: none Statistical analysis: none	Estimated exposure: >20 mg/m^3	Uranium workers had a “higher than expected” prevalence of SLE. Number of cases: - Definite (4+ diagnostic criteria): 28 - Probable (2–3 diagnostic criteria): 15 Estimated prevalence in uranium workers: - 93 in 100,000 Background incidence in male population: - Male population: 3.6 in 100,000 - Caucasian population: 20–50 in 100,000

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Steenland and Brown 1995b	Study design: historical cohort study Industry: gold miners Location: South Dakota, United States	Cohort: 3,328 workers employed for at least 1 year between 1940 and 1965, with follow-up until 1990 (mean exposure duration: 9 years) Adjustments: see statistical analysis Statistical analysis: life-table analysis (which accounts for age, race, sex, and time and calendar intervals for the U.S. population) with χ^2 tests	Median cumulative exposure (mg/m^3-year): 0.23[c]	The SMRs for deaths that listed the presence of "other" musculoskeletal diseases (including SLE and SSc) and "other" skin diseases (including SSc and SLE) were increased: Other musculoskeletal diseases: - Number of cases at death: 10 - SMR (95% CI): 2.14 (1.03, 3.94) Other diseases of the skin: - Number of cases at death: 10 - SMR (95% CI): 2.45 (1.17, 4.51) Note: The number of individual SLE or SSc cases was not specified.
Steenland et al. 2001b	Study design: historical cohort study Industry: industrial sand workers Location: United States (11 different states)	Cohort: 4,626 workers employed in 18 plants for at least 1 week from 1940s to 1980s and lived past 1960, with follow-up through 1996; 4,027 workers with adequate work histories to estimate exposure Adjustments: age, race, sex, calendar time Statistical analysis: standard life-table analysis	Mean cumulative exposure to respirable c-silica (mg/m^3-year): 0.13[b] Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: <0.10 (referent) Q2: 0.10–<0.51 Q3: 0.51–<1.28 Q4: ≥1.28	The SMR for deaths that listed the presences of "other" musculoskeletal diseases (including SLE and SSc) was not increased: - Number of cases at death: 8 - SMR (95% CI): 2.18 (0.93, 4.28) Note: Among the eight deaths reporting musculoskeletal diseases, three deaths reported SSc and one death reported SLE.

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Sarcoidosis				
Rafnsson et al. 1998	Study design: case-referent study Industry: diatomaceous earth plant Location: Husavik, Iceland	Cases: eight cases of sarcoidosis (four men, four women) diagnosed either at the healthcare center in the town of Husavik or at a routine occupational health examination at a diatomaceous earth plant in the district; diagnoses occurred between 1974 and 1993 Referents: 70 individuals selected randomly from the population of the district served by the Husavik health center/hospital Adjustments: the study authors did stratify for age; however, the age range of the cases determined the age section of the population register that was used to draw the referents Statistical analysis: Fisher's Exact Test	Mean exposure to respirable cristobalite in 1978 (mg/m^3): - Loading: 0.3 - Packers: 0.6 - Over operators: 0.3 - Maintenance men: 0.2 - Cleaners: 0.1 Mean exposure to respirable cristobalite in 1981 (mg/m^3): - Loading: 0.02 - Packers: 0.05 - Over operators: 0.002 - Maintenance men: 0.01 - Cleaners: 0.06	Number of total sarcoidosis cases with a history of exposure (employed at diatomaceous earth plant): 6/8 Number of incidental sarcoidosis cases diagnoses at the healthcare center (not part of routine occupational health exam) with a history of exposure: 4/6 Number of referents with a history of exposure (employed at diatomaceous earth plant): 13/70 The risk of both total and incidental sarcoidosis cases were increased in exposed individuals. ORs (95% CI): - Total: 13.2 (2.0, 140.9) - Incidental: 8.8 (1.1, 102.5) Estimated annual incidence of sarcoidosis: - Population of Husavik region: 9.3/100,000 - Total population of Iceland: 0.5–2.7/100,000 Note: The six cases with c-silica exposure were distributed into different job categories; therefore, increased risk was not associated with a specific job.

Table 2-13. Autoimmune Disease in Workers Exposed to Respirable c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Vihlborg et al. 2017	Study design: retrospective cohort Industry: iron foundries Location: Sweden	Cohort: 2,187 male workers employed in 10 foundries, with employment for at least 1 year and beginning before 2005 Adjustments: none reported Statistical analysis: SIRs calculated using Poisson distribution of observed numbers	Cumulative exposure quartiles for respirable c-silica (mg/m^3-year): Q1: 0.012–0.023 Q2: 0.024–0.035 Q3: 0.036–0.047 Q4: ≥0.048	The risk of sarcoidosis was increased in the highest exposure quartile. SIR (95% CI): Q1: - (0 observed) Q2: 0.74 (0.02, 4.12) Q3: 1.62 (0.20, 5.84) Q4: 3.94 (1.07, 10.08)

[a]Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication), based on data provided by the original investigators.
[b]Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication) for Steenland and Sanderson. (2001), using the same cohort of industrial sand workers as Steenland et al. (2001b). Estimates were based on job-exposure matrices data provided by the original investigators.
[c]Exposures were estimated by Mannetje et al. (2002a, 2002b) (not reported in original publication), based on job-exposure matrices data provided by the original investigators.

CI = confidence interval; OR = odds ratio; SD = standard deviation; SIR = standard incidence ratio; SMR = standard mortality ratio; SRR = standardized rate ratio

Table 2-14. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies

Studies		Methods	Outcomes for meta-analysis
Bonvenzi et al. 1995 (case-control) - Cases: 5 males, 16 females - Controls: 10 males, 32 females (age- and sex-matched) - Location: Trento, Italy - Exposure: occupational history - OR (95% CI): 5.20 (0.48, 74.1) Bonvenzi et al. 2004 (case-control) - Cases: 9 males, 46 females - Controls: 18 males, 153 females (age- and sex-matched) - Location: Verona, Italy - Exposure: occupational history - RR (95% CI): 1.7 (0.4, 7.6) Burns et al. 1996 (case-control) - Cases: 274 females - Controls: 1184 females (age-, race-, and region-matched) - Location: Michigan, United States - Exposure: self-reported past exposure (job/hobby history), c-silica exposure in abrasive grinding/sandblasting, pottery making, and dental laboratories - OR (95% CI): 1.50 (0.76, 2.93)	Silman and Jones 1992 (case-control) - Cases: 56 males - Controls: 86 males (age-matched) - Location: United Kingdom - Exposure: occupational history - OR (95% CI): 1.40 (0.12, 16.1) Brown et al. 1997 (cohort) - Silicosis patients: 1,130 men - Location: Sweden - Exposure: diagnosis of silicosis as proxy for c-silica exposure - Number of scleroderma cases: 5 - RR (95% CI): 37 (11.9, 86.3) Mehlhorn et al. 1999 (cohort) - Uranium mine workers: 243,900 men with “high” exposure and 50,000 men with “low” exposure - Location: Germany - Exposure: “high” versus “low;” levels not reported - Number of scleroderma cases: not available - RR (95% CI): 7.41 (6.14, 8.93)	Selection of studies: Medline, Toxline, BIOSIS, and Embase searches were performed to identify studies evaluating the association between c-silica exposure and SSc published between 1949 and November 2009. Of the 20 studies identified, only 16 studies had measures of RR (OR, SIR, SMR, or PMR) or sufficient data for calculation of RR for SSc in c-silica-exposed workers. A total of 16 studies including 1,030,152 subjects were selected (781,882 men, 233,324 women, 14,946 sex not specified). Data analysis: Measures of RRs and 95% CI were abstracted from data presented in primary reports. A meta-analysis was conducted using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group’s recommendations. Heterogeneity of the studies were analyzed using Cochran Q and I^2 statistics. The CERR and 95% CI were	All studies: An increased risk of SSc with c-silica exposure was identified; studies showed significant heterogeneity. CERR (95% CI): - Both sexes: 3.20 (1.89, 5.43) Stratified by sex: An increased risk of SSc with c-silica exposure was identified in men, but not in women; male data showed significant heterogeneity and female data showed nonsignificant heterogeneity. CERR (95% CI): - Men: 3.02 (1.24, 7.35) - Men (two studies excluded): 2.06 (1.04, 4.08) - Females: 1.03 (0.74, 1.44) Stratified by location: An increased risk of SSc with c-silica exposure was identified in European studies, but not in studies conducted in the United States. Data for both locations showed significant heterogeneity.

Table 2-14. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies

Studies		Methods	Outcomes for meta-analysis
Diot et al. 2002 (case-control) - Cases: 11 males, 69 females - Controls: 22 males, 138 females (age-, sex-, and smoking-habit-matched) - Location: France - Exposure: occupational history - OR (95% CI): 5.57 (1.69, 18.37) Englert et al. 2000 (case-control) - Cases: 160 males - Controls: 83 males (age- and region-matched) - Location: Australia - Exposure: occupational history (c-silica exposure in construction, mining, and manufacturing) - OR (95% CI): 2.51 (1.28, 4.98) Lacey et al. 1997 (case-control) - Cases: 189 females - Controls: 1,043 females (age-, race-, and region-matched) - Location: Ohio, United States - Exposure: self-reported past exposure (job/hobby history) - OR (95% CI): 0.87 (0.19, 4.0)	Rosenman et al. 1999 (cohort) - Silicosis patients: 583 men and women - Location: United States - Exposure estimate: diagnosis of silicosis as proxy for c-silica exposure - Number of scleroderma cases: 1 - RR (95% CI): 15.65 (0.21, 87.03) Calvert et al. 2003 (mortality) - 17,238 deaths - Location: United States - Exposure estimate: job title (high c-silica exposure in drillers, crushing and grinding machinists, miners, pottery workers, and foundry workers) - Number of scleroderma cases: 976 males, 1,899 females - OR (95% CI): 2.00 (0.39, 10.31) Gold et al. 2007 (mortality) - 72,732 male and 197,479 female deaths - Location: United States - Exposure estimate: job title - Number of scleroderma cases: 1,298 males, 4,344 females - OR (95% CI): 1.02 (0.92, 1.13)	calculated using fixed or random effect models. Further analysis were conducted on studies stratified by sex, location, publication date, and study design. An additional analysis in men only was conducted with two studies excluded (Mehlhorn et al. 1999 and Ziegler et al. 1997) in order to reduce bias. These studies were excluded because they did not use a typical cohort or case-control design; rather, they started historically with a case series and tried to construct a study post-hoc.	CERR (95% CI): - Europe: 5.91 (3.06,11.42) - United States: 1.23 (0.97, 1.56) <u>Stratified by publication date</u>: An increased risk of SSc with c-silica exposure was identified in studies published prior to 2000, but not in 2000 or later. Data for both time periods showed significant heterogeneity. CERR (95% CI): - Pre-2000: 4.22 (1.64, 10.86) - Since 2000: 1.96 (0.95, 4.07) <u>Stratified by study design</u>: An increased risk of SSc with c-silica exposure was identified in in case-control studies and cohort studies, but not the case-series study. Cohort studies showed significant heterogeneity; case-control and case-series studies showed nonsignificant heterogeneity.

Table 2-14. Meta-Analysis of Relative Risk for Systemic Sclerosis (SSc) in a Pooled Analysis of 16 Epidemiological Studies

Studies		Methods	Outcomes for meta-analysis
Maître et al. 2004 (case-control) - Cases: 10 men, 83 women - Controls: 40 men, 166 women (age- and sex-matched) - Location: France - Exposure: based on job title - RR (95% CI): 0.89 (0.26, 3.2) Rodnan et al. 1967 (case-control) - Cases: 60 males - Controls: 86 males (age- and race-matched) - Location: United States - Exposure: based on job title (c-silica exposure in coal miners, sandblasters, rock drillers, brick molders, and foundry, enamel, pottery, and cement factory workers) - RR (95% CI): 3.34 (1.59, 7.05)	Walsh 1999 (mortality) - 411,404 male and 30,563 female deaths - Location: United States - Exposure estimate: job title (c-silica exposure in mining machine operators and numerous non-mining jobs such as brick/stone mason, grinders/polishers, various construction workers) - Number of scleroderma cases: 128 males, 32 females - PMR (95% CI): 1 (0.80,1.10) Ziegler et al. 1997 (case series) - Cases: 54 males - Location: Germany - Exposure: occupational history - RR (95% CI): 10.40 (6.10, 17.8)		CERR (95% CI): - Case-control: 2.24 (1.65, 3.31) - Cohort: 15.49 (4.54, 52.87) - Mortality studies: 1.01 (0.94, 1.08)

CERR = combined estimator of relative risk; CI = confidence interval; OR = odds ratio; PMR = proportionate mortality ratio; RR = relative risk or risk ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Source: McCormic et al. (2010)

females (CERR: 1.03; 95% CI: 0.74, 1.44). Additional analysis indicated that increased risk was predominantly due to studies published prior to 2000 (CERR: 4.22; 95% CI: 1.64, 10.86), with more recent studies not showing an increased risk for SSc (CERR: 1.96; 95% CI: 0.95, 4.07). Location of study was also an important factor, with an increased risk of SSc in c-silica-exposed individuals in European studies (CERR: 5.91; 95% CI: 3.06, 11.42), but not U.S. studies (CERR: 1.23; 95% CI: 0.97, 1.56). Results of this meta-analysis indicate that c-silica exposure may increase the risk of SSc in men; however, available data are inadequate to determine the exposure-response relationship.

Rheumatoid arthritis (RA). Three studies providing exposure data have evaluated the risk of RA in c-silica-exposed workers (see Table 2-13 for study details). The incidence of RA was significantly ($p<0.001$) increased in a cohort of male granite workers exposed to quartz particles (<5 μm diameter) at an estimated geometric mean exposure concentration of 0.82–1.47 mg/m^3, with an incidence rate of 1.69/1,000 (0.2%) compared with that of the general population (0.24/1,000; (0.02%) (Klockars et al. 1987; Koskela et al. 1987b). However, the risk of RA was not increased in a cohort of male and female workers from pottery or related industries exposed to mean air levels of respirable c-silica of 0.1329 mg/m^3 (Turner and Cherry 2000). A nested case-referent study in the same cohort showed that estimated mean cumulative exposure to respirable c-silica did not differ between cases (2.525 mg/m^3-year) and referents (2.872 mg/m^3-year). The risk of RA was increased in Swedish, male iron foundry workers in the highest estimated cumulative exposure quartile (≥0.048 mg/m^3-year), based on an SIR of 2.58 (95% CI: 1.24, 4.76) (Vihlborg et al. 2017).

Two additional occupational studies with exposure information evaluated the risk of arthritis (including RA) in c-silica-exposed workers; however, these studies are of limited usefulness based on methods of analysis (e.g., grouping RA with osteoarthritis); study details are provided in Table 2-13. Steenland and Brown (1995b) reported a 2.19-fold (95% CI: 1.27, 3.50) increase in the presence of arthritis (including RA) at death in gold miners exposed to mean cumulative respirable c-silica levels of 11.37 mg/m^3-year, and Steenland et al. (2001b) reported a 4.36-fold (95% CI: 2.76, 6.54) increase in the presence of arthritis (including RA) at death in industrial sand workers exposed to mean cumulative respirable c-silica levels of 0.13 mg/m^3-year (exposure estimates calculated by Mannetje et al. 2002b). When analyzed by exposure quartile, a positive trend was observed for arthritis (including RA) in the sand workers cohort (slope: 0.00018; 95% CI: 0.00017, 0.00019); exposure by quartile was not assessed in gold miners. The numbers of arthritis cases were 17 in gold miners and 23 in sand workers. Steenland et al. (2001b) also reported the specific number of RA cases (12) in sand workers; however, SMR analysis was not conducted specifically for RA. Additionally, a study lacking exposure information reported a 2.01-fold

(95% CI: 1.17–3.21) increase in the presence of arthritis (including RA) at death for male granite workers in a mortality cohort (Steenland et al. 1992). The number of arthritis cases in this cohort was 17.

Several additional studies reported a 2–8-fold increase in risk or incidence of RA in cohorts of men with occupational exposure to c-silica, the majority of which were diagnosed with silicosis; however, these studies did not provide quantitative estimates of exposure (Brown et al. 1997; Makol et al. 2011; Rosenman and Zhu 1995; Rosenman et al. 1999; Stolt et al. 2005, 2010). A case-referent study of c-silica-exposed miners showed an increased risk of RA in miners with silicosis compared with c-silica-exposed miners without silicosis, although these findings could not be accounted for based on estimates of cumulative exposure (c-silica exposure levels not reported) (Sluis-Cremer et al. 1986). Results of cohort mortality yielded conflicting results; Calvert et al. (2003) reported an increased OR for RA in c-silica-exposed workers with "high silica exposure," including miners, crushing and grinding machine workers, pottery workers, and foundry workers, while no increase was observed in workers with potential c-silica exposure from various industries (based on work history and job-exposure matrix) (Gold et al. 2007).

Taken together, available evidence indicates that c-silica exposure may increase the risk of RA; however, available data are inadequate to determine an exposure-response relationship.

Systemic lupus erythematosus (SLE). Two studies providing exposure data have evaluated the risk of SLE in c-silica-exposed workers (Steenland and Brown 1995b; Steenland et al. 2001b); see Table 2-13 for study details. However, these studies are of limited usefulness based on methods of analysis (e.g., grouping SLE with related disorders, statistical analysis not conducted). The incidence of SLE was "higher than expected" in a 15,000 group of "heavily exposed" (>20 mg/m^3) uranium miners with silicosis, with 28 definite cases (4+ American Rheumatism Association [ARA] criteria) and an additional 15 probable cases (2–3 ARA criteria) (Conrad et al. 1996). Based on these findings, the estimated prevalence of SLE was 93 in 100,000 in uranium workers, compared with the background incidence of 3.6 in 100,000 in the male population and 20–50 in 100,000 in the general Caucasian population (Conrad et al. 1996). In gold miners exposed to mean cumulative respirable c-silica levels of 11.37 mg/m^3-year, the incidences of "other musculoskeletal diseases" and "other diseases of the skin" at death (including SLE) were increased by 2.14-fold (95% CI: 1.03, 3.94) and 2.45-fold (95% CI: 1.17, 4.51), respectively (Steenland and Brown 1995b; exposure estimates calculated by Mannetje et al. 2002b). However, the incidence of SLE, specifically, was not reported or analyzed. In industrial sand workers exposed to lower cumulative levels of respirable c-silica (0.13 mg/m^3-year), the incidence of "other musculoskeletal

diseases" (including SLE) was not increased (Steenland et al. 2001b; exposure estimates calculated by Mannetje et al. 2002b).

Other available case-control and cohort studies reported inconsistent findings; however, these studies did not provide quantitative cumulative exposure estimates or exposure-response data. Two population-based case-control studies reported a 1.6–4-fold increase in risk of SLE diagnosis in individuals with a history of occupational exposure to c-silica (Cooper et al. 2010; Finckh et al. 2006). Women exposed for >5 years had an increased risk (OR: 4.9; 95% CI: 1.1, 21.9) compared to women exposed for 1–5 years (OR: 4.0; 95% CI: 1.2, 12.9); these findings showed a significant duration-related trend (p=0.01) (Finckh et al. 2006). Additionally, the relative risk for SLE was increased 24-fold in a cohort of men with silicosis (Brown et al. 1997). In this cohort, a 6-fold excess mortality from musculoskeletal diseases, including RA, SLE, and Sjogren's syndrome, was identified (6/1130 deaths, 0.5%) (Brown et al. 1997). However, the incidence of SLE was not elevated in other cohorts of patients with silicosis (Makol et al. 2011; Rosenman et al. 1999) and the incidence of SLE at death was not elevated in c-silica-exposed individuals (Calvert et al. 2003; Gold et al. 2007).

Taken together, available data are inadequate to determine if there is an association between c-silica exposure and increased risk of SLE.

ANCA-associated vasculitis (AAV). Studies evaluating the potential association between AAV and c-silica exposure did not report quantitative exposure data. Using studies with qualitative measures of exposure (e.g., occupational history), a meta-analysis of six case-referent studies showed increased OR for AAV (OR: 2.57; 95% CI: 1.15, 4.36) and AAV with renal involvement (OR: 3.13; 95% CI: 1.63, 5.84) in c-silica-exposed workers (Gomez-Puerta et al. 2013; study details provided in Table 2-15). Additional analysis showed that OR for specific AAV-associated diseases were also increased, including GPA (OR: 3.56; 95% CI: 1.85, 6.82) and MPA (OR: 3.95; 95% CI: 1.89, 8.24). However, when studies were stratified into those that adjusted for smoking status and occupational risk (n=2) and those that did not (n=4), studies with unadjusted OR showed an increase in risk of AAV with c-silica exposure (OR: 2.99; 95% CI: 1.43, 6.25), but studies with adjusted OR did not (OR: 2.24; 95% CI: 0.74, 6.80). Individually, four of the case-control studies used in the meta-analysis reported an increase in AAV risk in c-silica exposed individuals (Gregorini et al. 1993; Hogan et al. 2001; Nuyts et al. 1995; Stratta et al. 2001b), while the other two did not (Hogan et al. 2007; Lane et al. 2003). After adjustment for smoking status and occupational risk factors, risk was no longer increased in the study by Hogan et al. (2001). Additional studies not included in the meta-analysis also reported an increase in the incidence of AAV or

Table 2-15. Meta-Analysis of Relative Risk for ANCA-Associated Vasculitis (AAV) in a Pooled Analysis of Six Case-Control Studies

Studies		Methods	Outcomes for meta-analysis
Gregorini et al. 1993 - Cases: 16 patients with ANCA-positive glomerulonephritis - Controls: 32 patients with nephropathy without vasculitis (age- and date-of-admission-matched) - Location: Italy - Exposure: occupational history - OR (95% CI): 14.0 (1.7, 113.8) - Quality score: S2/C1/E1 Hogan et al. 2001 - Cases: 65 patients with ANCA-associated vasculitis - Controls: 65 patients with nephropathy without vasculitis (age-, sex-, and region-matched) - Location: United States - Exposure: occupational history - Adjusted OR (95% CI): 4.43 (1.36,14.4) - Quality score: S3/C1/E1 Hogan et al. 2007 - Cases: 129 patients with ANCA-positive glomerulonephritis - Controls: 109 randomly selected age-, sex-, and state-matched individuals - Location: United States - Exposure: occupational history - OR (95% CI): 1.6 (0.9, 2.8) - Quality score: S3/C1/E1	Lane et al. 2003 - Cases: 75 patients with primary systemic vasculitis - Controls: 220 patients with non-inflammatory musculoskeletal disease (age- and sex-matched) - Location: United Kingdom - Exposure: occupational history - OR (95% CI): 1.4 (0.7, 2.7) - Adjusted OR (95% CI): 1.4 (0.73, 6.79) - Quality score: S2/C2/E2 Nuyts et al. (1995 - Cases: 16 patients with granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) - Controls: 32 randomly selected age-, sex-, and region-matched individuals - Location: Belgium - Exposure: occupational history - OR (95% CI): 5.0 (1.4, 11.6) - Quality score: S3/C1/E2 Stratta et al. 2001b - Cases: 31 patients with renal vasculitis - Controls: 58 patients with nephropathy without vasculitis - Location: Italy - Exposure: occupational history - OR (95% CI): 2.4 (1.02, 6.5) - Quality score: S2/C1/E1	Selection of studies: EMBASE and MEDLINE searches were performed to identify case-control and cohort studies evaluating the association between c-silica exposure and ANCA-associated vasculitis published between January 1965 and April 2013. Studies were assessed for quality using the Newcastle-Ottawa Scale; quality scores were assigned based on selection of comparison groups (S; 0–4 points), comparability between the two groups (C; 0–2 points), and exposure ascertainments (E; 0–3 points). Data analysis: OR were abstracted from published reports. Two studies reported adjusted OR (adjusted for smoking status and occupational risk factors). Heterogeneity of the studies was analyzed using Q and I^2 statistics. Data showed significant heterogeneity, so OR and 95% CI were calculated using random effect models. Further analyses were conducted on studies stratified by OR adjustment and renal involvement. Comprehensive meta-analysis software	The risk of AAV and AAV with renal involvement was increased in c-silica-exposed individuals. OR (95% CI): - All studies: 2.57 (1.15, 4.36) - AAV with renal involvement: 3.13 (1.68, 5.84) - GPA[a]: 3.56 (1.85, 6.82) - MPA[b]: 3.95 (1.89, 8.24) Studies reporting unadjusted estimates of association showed an increased risk of AAV in c-silica-exposed individuals, but studies that adjusted for smoking and occupational risk factors did not. OR (95% CI): - Unadjusted studies: 2.99 (1.43, 6.25) - Adjusted studies: 2.24 (0.74, 6.80)

Table 2-15. Meta-Analysis of Relative Risk for ANCA-Associated Vasculitis (AAV) in a Pooled Analysis of Six Case-Control Studies

Studies	Methods	Outcomes for meta-analysis
	(www.meta-analysis.com; ©Biostat, Inc.) was used for statistical analysis.	

[a]GPA = granulomatosis with polyangiitis (formerly Wegener granulomatosis).
[b]MPA = microscopic polyangiitis.

ANCA = antineutrophil cytoplasmic antibodies; CI = confidence interval; OR = odds ratio

Source: Gomez-Puerta et al. (2013)

ANCA-positivity with a history of c-silica exposure, including two silicosis cohort studies (Bartunkova et al. 2006; Makol et al. 2011) and two case-referent studies (Beaudreuil et al. 2005; Rihova et al. 2005).

Based on the meta-analysis, evidence suggests that c-silica exposure may increase the risk of AAV; however, the lack of exposure-response data and the lack of increased risk following adjustments for smoking and occupational risk factors preclude the ability to determine if there is an association between c-silica exposure and increased risk of AAV.

Sarcoidosis. The risk of sarcoidosis was increased in Swedish, male iron foundry workers in the highest cumulative exposure quartile (≥0.048 mg/m^3-year), based on an SIR of 3.94 (95% CI: 1.07, 10.08) (Vihlborg et al. 2017). In a case-referent study, the risk of sarcoidosis was increased 13-fold (95% CI: 2.0, 140.9) in men and women exposed to c-silica at a diatomaceous earth plant in the Husavik region of Iceland; estimated mean exposure levels to respirable cristobalite at the plant ranged from 0.002 to 0.06 mg/m^3; see study details in Table 2-13 (Rafnsson et al. 1998). The annual incidence of sarcoidosis in the Husavik region was estimated to be 9.3 per 100,000, compared to the national average of 0.5–2.7 per 100,000 (Rafnsson et al. 1998). A study evaluating the potential association between c-silica exposure and sarcoidosis found a decreased risk of sarcoidosis in c-silica-exposed individuals in a mortality cohort (OR: 0.66; 95% CI: 0.54, 0.80) (Calvert et al. 2003), and a statistically significant decrease in the risk of sarcoidosis-related mortality was observed in silica workers in the United States (mortality OR: 0.65; 95% CI: 0.42, 0.74; $p<0.05$) (Liu et al. 2016). Available data are inadequate to determine if there is an association between c-silica exposure and increased risk of sarcoidosis.

Crystalline Silica, Oral. No studies evaluating immunological or lymphoreticular effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating immunological or lymphoreticular effects in humans following inhalation exposure to a-silica were identified.

No treatment-related changes in immune organ weight or histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). No changes in spleen or lymph node histology were observed in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981). In monkeys,

no significant changes in spleen weight or histology were observed following exposure to precipitated a-silica at 15 mg/m^3 for 8 hours/day, 5 days/week for up to 12 months (Schepers 1962).

Amorphous Silica, Oral. No studies evaluating immunological or lymphoreticular effects in humans following oral exposure to a-silica were identified.

A significant 18% decrease in spleen weight was observed in female F344 rats exposed to dietary a-silica gel at 2,410 mg/kg/day for 26 weeks (Takizawa et al. 1988). Spleen weights were not decreased in female F344 rats at ≤1,160 mg/kg/day or male F344 rats at doses up to 2,220 mg/kg/day, and no treatment-related histopathological lesions were reported (Takizawa et al. 1988). No significant changes in thymus or spleen weight or histology were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the lymph nodes. In B6C3F1 mice, a significant 20% decrease in spleen weight was observed in males exposed to a-silica gel at a dietary dose of 6,700 mg/kg/day for 26 weeks (Takizawa et al. 1988). Spleen weights were not decreased in male B6C3F1 mice at ≤3,280 mg/kg/day or female B6C3F1 mice at doses up to 2,220 mg/kg/day, and no treatment-related histopathological lesions were reported (Takizawa et al. 1988).

No changes in spleen histology were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). Similarly, no significant changes in spleen weight or histology were observed in F344 rats exposed to a-silica gel at dietary doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no significant changes in spleen weight or histology were observed following exposure to a-silica gel at dietary doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

2.15 NEUROLOGICAL

Crystalline Silica, Oral. Silica levels in drinking water were not associated with cognitive impairment using the Mini-Mental State Examination (MMSE) in 3,777 French subjects >65 years of age; median silica (form not specified, assumed to be c-silica) levels in drinking water were 11.2 mg/L (range 4.2–22.4 mg/L) (Jacqmin-Gadda et al. 1996). Using a reference water intake of 1.046 L for populations >65 years of age and a reference body weight of 80 kg (EPA 2011), estimated mean daily intakes were calculated to be 0.15 mg/kg/day (range 0.05–0.29 mg/kg/day). These findings were supported by a

second study, which found an inverse association between silica (form not specified, assumed to be c-silica) levels in drinking water and cognitive impairment in the Short Portable Mental Status Questionnaire in 7,598 French females ≥75 years of age; the average daily intake was of 10.17 mg/day (Gillette-Guyonnet et al. 2005). Using reference body weight of 80 kg (EPA 2011), daily intakes were calculated to be 0.13 mg/kg/day for this study. A 5-year follow-up study in this cohort indicated that women with low silica intake (≤4 mg/day) had a 2.7-fold increased risk of Alzheimer's disease (OR: 2.74; 95% CI: 1.09, 6.86), while high silica intake (9–12 mg/day) was not associated with Alzheimer's disease (OR: 2.00; 95% CI: 0.56, 7.07) (Gillette-Guyonnet et al. 2005).

No studies evaluating neurological effects in animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating neurological effects in humans following inhalation exposure to a-silica were identified. No changes in brain weight or central or peripheral nervous tissue histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991).

Amorphous Silica, Oral. No studies evaluating neurological effects in humans following oral exposure to a-silica were identified. No clinical signs of neurotoxicity or exposure-related changes in brain weight or histology were observed in Wistar rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day for approximately 18 weeks (Wolterbeek et al. 2015) or pyrogenic a-silica at a dietary dose of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Similarly, no clinical signs of neurotoxicity or significant changes in brain weight or histology were observed in F344 rats or B6C3F1 mice exposed to a-silica gel at dietary doses up to 2,410 or 9,810 mg/kg/day, respectively, for 26 weeks (Takizawa et al. 1988).

No clinical signs of neurotoxicity were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of100 mg/kg/day for 24 months (Lewinson et al. 1994). No clinical signs of neurotoxicity or significant changes in brain weight or histology were observed in F344 rats exposed to a-silica gel at dietary doses up to 2,200 mg/kg/day for 52 weeks or 2,010 mg/kg/day for 103 weeks (Takizawa et al. 1988). In B6C3F1 mice, no clinical signs of neurotoxicity or significant changes in brain weight or histology were observed following exposure to a-silica gel at dietary doses up to 7,560 mg/kg/day for 52 weeks or 6,010 mg/kg/day for 93 weeks (Takizawa et al. 1988).

2.16 REPRODUCTIVE

Crystalline Silica, Oral. One case-control study in the Boston area suggests a potential increase in the risk of spontaneous abortion and high silica content in public drinking water (Aschengrau et al. 1989); however, the confidence in these findings is low due to a variety of study limitations, which are discussed below. In this study, the potential relationship between spontaneous abortion and drinking water quality was evaluated in 286 women with spontaneous abortions through 27 weeks of gestation and 1,391 women with live births in Boston and surrounding areas. Potential exposure to routinely monitored chemicals and metals in drinking water, including an unspecified form of silica (assumed to be c-silica), was estimated based on routinely collected community drinking water data using residential address at the time of pregnancy and water data at a time-point nearest to conception. The interval from the date of the matched water sample to the time of conception for study participants (cases and controls combined) ranged from 0 to 872 days for silica content; the median interval was 65 days. Community drinking water samples generally came from public buildings, such as a town hall; no residential drinking water samples were evaluated and no water consumption data or habits were assessed. The potential risk of spontaneous abortion was evaluated for silica after adjusting for other trace elements (arsenic, chromium, lead, mercury, sodium, potassium, iron, sulfate, chloride, nitrate, and copper) and water characteristics (pH, alkalinity, hardness, Langelier index, and water source). For adjusted analysis, the study authors excluded subjects residing within Boston (39.5% of cases, 34.9% of controls) due to potential confounding factors for residents of Boston that were not controlled for in the study, leaving 1,078 subjects for analysis. The adjusted OR for the highest silica tertile (3.7–32.0 mg/L) was increased compared to the lowest tertile (0–2.7 mg/L); OR: 1.9, 95% CI: 1.1, 3.2. The risk of spontaneous abortion was not increased in the middle tertile (2.8–3.6 mg/L); OR: 0.5; 95% CI: 0.3, 0.8. Other trace elements associated with increased risk of spontaneous abortion in this study included any detectable levels of mercury and high levels of arsenic or potassium. This study has numerous limitations that decrease confidence in the findings, including: (1) use of general public water data as a surrogate for residential exposure; (2) use of water data that, in some cases, was measured outside of pregnancy dates; (3) lack of actual water consumption data and/or habits; (4) ad-hoc exclusion of Boston residents, which represented 36% of the original subject pool; and (5) lack of control for unmeasured water quality parameters (e.g., organic contaminants, groundwater treatment) and other environmental exposures.

No studies evaluating reproductive effects in animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating reproductive effects in humans following inhalation exposure to a-silica were identified.

No studies evaluating reproductive function following inhalation exposure to a-silica were identified. In an intermediate-duration study, no changes in male or female reproductive organ weight or histology were observed in rats exposed to pyrogenic or precipitated a-silica at concentrations up to 30 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991). In a chronic-duration study, no changes in testicular or prostate histology were observed in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at concentrations up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months, compared with controls (Groth et al. 1981).

Amorphous Silica, Oral. No studies evaluating reproductive effects in humans following oral exposure to a-silica were identified.

Reproductive performance was not impaired in a 2-generation study in Wistar rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day for 10 weeks premating, through mating, gestation, and lactation (approximately 18 weeks total) (Wolterbeek et al. 2015). No exposure-related changes in mating, fertility, fecundity, gestation, live-birth, or viability indices were observed in F0 or F1 animals. Precoital time, gestation time, postimplantation loss, and total litter losses were comparable to control. Additionally, no changes in sexual maturation or estrous cyclicity of F1 animals were observed. Sperm parameters in exposed F0 and F1 adults were also comparable to controls.

In a 1-generation study, reproductive performance was not impaired during the generation of two litters in male and female Wistar rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day for a total of 6 months; mating for the first litter occurred after 8 weeks of exposure and mating for the second litter occurred after 17 weeks of exposure (Lewinson et al. 1994). There were no significant changes in the breeding rate, number of pregnant females, number of live and dead pups, or mean litter size in exposed rats, compared with controls.

In an intermediate-duration study, no significant changes in testes or ovary weight or histology were observed in Wistar male and female rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day for 6 months, compared with controls (Lewinson et al. 1994). Additionally, no histopathological changes were observed in the uterus (uterus weight not recorded). In a chronic-duration study, no changes in

testes, ovary, or uterus histology were observed in Wistar rats exposed to pyrogenic a-silica at a dietary dose of 100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994).

2.17 DEVELOPMENTAL

Crystalline Silica, Oral. No studies evaluating developmental effects in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. No studies evaluating developmental effects in humans or animals following inhalation exposure to a-silica were identified.

Amorphous Silica, Oral. No studies evaluating developmental effects in humans following oral exposure to a-silica were identified.

No evidence of developmental toxicity was observed in a 2-generation study in Wistar rats exposed to precipitated a-silica at gavage doses up to 1,000 mg/kg/day for 10 weeks premating, through mating, gestation, and lactation (approximately 18 weeks total) (Wolterbeek et al. 2015). There were no exposure-related changes in the live birth or viability indices, sex ratio, pup weight or growth, gross pup abnormalities, or thorough necropsy at PND 21. In a 1-generation study, there were no significant changes in mean birth weight, number of runts, gross pup abnormalities at birth, growth or survival during lactation, or gross pathological findings at the postnatal week 4 sacrifice from the first or second litter produced by male and female Wistar rats exposed to pyrogenic a-silica at a dietary dose of 500 mg/kg/day for a total of 6 months, compared with controls (Lewinson et al. 1994). Mating for the first litter occurred after 8 weeks of exposure, and mating for the second litter occurred after 17 weeks of exposure.

2.18 CANCER

Crystalline Silica, Inhalation. Well over 100 studies examining the relationship between occupational exposure to c-silica and lung cancer have been published, including several recent reviews (Brown 2009; Checkoway and Franzblau 2000; Cox 2011; Gamble 2011; IARC 2012; NIOSH 2002; Soutar et al. 2000; Steenland 2005; Steenland and Ward 2014). The information reviewed in this section focuses on studies published after the 1997 IARC evaluation of c-silica.

Carcinogenicity Classifications Based on Lung Cancer. In 1997, IARC revised the classification of c-silica from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) citing sufficient evidence for carcinogenicity in humans and animals (IARC 1997). The IARC working group noted that "carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the c-silica or on external factors affecting its biological activity or distribution of its polymorphs." In 2012, IARC conducted a re-evaluation of the carcinogenicity of c-silica, incorporating data available after the 1997 assessment. IARC retained the Group 1 classification for c-silica, concluding that "there is sufficient evidence in humans for the carcinogenicity of c-silica in the form of quartz or cristobalite. C-Silica in the form of quartz or cristobalite dust causes cancer of the lung. There is sufficient evidence in experimental animals for the carcinogenicity of quartz dust." IARC (2012) also noted that c-silica is carcinogenic to rats following exposure by inhalation or intratracheal instillation, but no evidence of lung cancer has been observed in c-silica-exposed mice or hamsters; the basis of these species differences has not been established. NIOSH (2002) and the NTP 13th Report on Carcinogens (NTP 2014) also have concluded that c-silica (respirable size) is a human carcinogen.

Issues and Confounding Factors for Lung Cancer. The IARC (1997) Group 1 classification for c-silica was considered controversial due, in part, to inconsistent results of occupational exposure studies and the lack of exposure-response data (Brown 2009; Cox 2011; Gamble 2011; NIOSH 2002; Pelucchi et al. 2006; Soutar et al. 2000; Steenland 2005; Steenland and Ward 2014). The IARC working group 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. However, other confounding factors and biases may influence results from individual studies, including 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 (Chen et al. 2007). In addition, the occupational risk of lung cancer that has been attributed to c-silica exposure is low, requiring large study populations to achieve adequate power to detect and quantify c-silica-related cancer risk. Pooled and meta-analyses provide an approach to increasing explanatory power of the collective data, although such approaches do not necessarily address other types of limitations. Several pooled and meta-analyses have been published since the IARC (1997) evaluation, providing information on the exposure-response relationship between c-silica and lung cancer and the relationship between silicosis status and lung cancer.

Exposure-Response Data for Lung Cancer. Pooled and meta-analyses of the relationship between cumulative exposure to c-silica and lung cancer are summarized in Table 2-16 (Finkelstein 2000; Lacasse et al. 2009; Steenland et al. 2001a, 2005). Steenland et al. (2001a, 2005) conducted a pooled exposure-response analysis of 65,980 c-silica exposed workers from diatomaceous earth, granite, pottery, and mining industries. Silicosis status of each worker was undefined in the analysis. For the pooled cohort (estimated mean cumulative exposure: 4.27 mg/m^3-year), the SMR for lung cancer was 1.2 (95% CI: 1.1, 1.3), indicating a 20% increase in the risk of lung cancer. Increasing exposure was significantly associated with increased lung cancer risk. The exposure-response relationship for the pooled cohort stratified by estimated cumulative exposure quintiles (<0.4 [referent]; 0.4–2.0; 2.0–5.4, 5.4–12.8, and >12.8 mg/m^3-year) showed increased ORs for lung cancer at cumulative exposures >2.0 mg/m^3-year, based on both no lag time and a 15-year lag time. A significant positive trend was observed using the log of estimated cumulative exposure lagged for 15 years (p=0.015; coefficient=0.062). For a 45-year exposure to 0.1 mg/m^3, the estimated excess for death due to lung cancer was 1.1–1.7% above a background lifetime risk for death due to lung cancer of 3–6%. A meta-analysis of over 1.6 million c-silica-exposed workers with undefined silicosis status from diatomaceous earth, industrial sand, mining, foundry, quarry, and pottery industries showed an exposure-response relationship between cumulative c-silica exposure and lung cancer (Lacasse et al. 2009). For estimated cumulative exposures of 1.0 and 6.0 mg/m^3-year, estimated risk ratios (95% CI) were 1.22 (1.01, 1.47) and 1.84 (1.48, 2.28), respectively. The exposure-response relationship between cumulative exposure to c-silica and relative risk of lung cancer (no lag time) is shown in Figure 2-5. The study authors stated that results showed an exposure-response relationship with an estimated exposure threshold for lung cancer of >1.84 mg/m^3-year. Based on a meta-analysis of two studies, Finkelstein (2000) estimated increased risk ratios for estimated cumulative exposures ≥2.0 mg/m^3-year, with estimated RRs (95% CI) ranging from 1.15 (1.09, 1.20) to 1.74 (1.65, 1.82) for exposures ranging from 2.0 to 5 mg/m^3-year, respectively.

Lung Cancer and the Role of Silicosis. Numerous studies have explored the relationship between silicosis and increased risk of lung cancer (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). In general, lung cancer has been shown to increase in workers with and without silicosis; however, the association between workers with silicosis and lung cancer is stronger than for workers without silicosis. Details of recent meta- or pooled analyses providing information on the relationship between silicosis status and increased risk of lung cancer are provided in Table 2-17 (Erren et al. 2009b; Kurihara and Wada 2004; Pelucchi et al. 2006; Poinen-Rugooputh et al. 2016). The conclusion from

Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

Reference	Studies in analysis	Methods and estimated exposure	Outcomes
Finkelstein 2000	Hnizdo and Sluis-Cremer 1993 - Nested case-control study (data from Hnizdo and Sluis-Cremer 1991) - South Africa; gold miners Checkoway et al. 1997 - Cohort study - United States; diatomaceous earth workers	Study type: meta-analysis on lung cancer in c-silica-exposed workers with undefined silicosis status Literature search dates: not reported Adjustments: no adjustment for exposure to radon daughters in gold mining cohorts Statistical analysis: weighted least squares estimate of the regression slope of the logarithm of the OR (or RR) versus exposure was computed for each study; inverse of the variance of log (OR) used as the regression weight; regression slopes were combined using an inverse variance-weighted average Exposure: not reported	Slope (95% CI) of log (RR) versus lagged cumulative exposure (mg/m^3-year): - Hnzido et al. 1997: 0.48 (0.18, 0.78); lagged 20 years - Checkoway et al. 1997: 0.10 (0.01, 0.20); lagged 15 years - Weighted average: 0.14 (0.05, 0.23) Estimated RR of lung cancer relative to cumulative exposure for lifetime exposure to respirable c-silica: - 1 mg/m^3-year: 1 - 2 mg/m^3-year: 1.15 (1.09, 1.20) - 3 mg/m^3-year: 1.32 (1.26, 1.38) - 4 mg/m^3-year: 1.51 (1.44, 1.59) - 5 mg/m^3-year: 1.74 (1.65, 1.82)
Lacasse et al. 2009	Cohort studies: Checkoway et al. 1997 (United States; diatomaceous earth workers); Steenland and Sanderson 2001 (United States; industrial sand workers); Brown and Rushton 2005b (United Kingdom; industrial sand workers); Pukkala et al. 2005 (Finland; miscellaneous) Case-control studies: Ulm et al. 1999 (Germany; miners, foundry and quarry workers); Bruske-Hohlfeld et al. 2000 (China; miners and pottery workers); Cocco et al. 2001 (China; miners and pottery workers); Chen et al. 2007 (China; miners and pottery workers); Westberg and Bellander 2003 (Sweden; aluminum foundry workers); Hughes et al. 2001 [updated by McDonald et	Study type: dose-response meta-analysis examining the relationship between cumulative exposure (mg/m^3-year) to c-silica and lung cancer in workers with undefined silicosis status Literature search dates: 1966–December 2007 Statistical analysis: data from all studies were pooled into a joint analysis; spline regression models were used; heterogeneity between different studies was modeled by an additional random component of variance; responses were evaluated for no lag time; post-hoc analysis of	Number of c-silica-exposed workers in all cohort studies: 1,608,635[a] Number of workers in all case control studies: 1,726 cases; 4,746 controls Results including all studies: Heterogeneity was observed across studies. The risk of lung cancer increased with increasing exposure to c-silica. Estimated RR (95% CI) for cumulative exposures of: - 1.0 mg/m^3-year: 1.22 (1.01, 1.47) - 6.0 mg/m^3-year: 1.84 (1.48, 2.28)

Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

Reference	Studies in analysis	Methods and estimated exposure	Outcomes
	al. 2005] (United States; industrial sand workers)	subset of more homogenous studies was conducted Exposure: not reported for overall cohort or individual studies	Estimated threshold for lung cancer: >1.84 mg/m^3-year Post-hoc analysis of a subset of more homogenous studies (n=8; excluding Ulm et al. 1999 and Hughes et al. 2001) revealed similar results (numeric data not reported). Study authors note that interpretation of results "is however limited by the wide range of exposure to respirable c-silica reported in the original studies, the heterogeneity across studies, and the confounding effect of silicosis that cannot be fully assessed."
Steenland 2005; Steenland et al. 2001a	10 Cohorts I - C1: Checkoway et al. 1997; United States; diatomaceous earth workers (non-mine) - C2: Koskela et al. 1994: Finland; granite workers (non-mine) - C3:Costello and Graham (1998); United States; granite workers (non-mine) - C4: Steenland et al. 2001a; United States; industrial sand workers (non-mine) - C5: Chen et al. 1992; China; pottery workers (non-mine) - C6: Chen et al. 1992; China; tin miners - C7: Chen et al. 1992: China; tungsten miners - C8: Hnizdo et al. 1997; South Africa; gold miners	Study type: pooled exposure-response analysis examining the relationship between cumulative exposure (mg/m^3-year) to c-silica and lung cancer in workers with undefined silicosis status Literature search dates: not reported Adjustments: not applicable Statistical analysis: nested case-control analyses using conditional logistic regression; matched for age, race, sex, date of birth; excess lifetime risk estimated by spline model with 15-year lag Median cumulative exposure (mg/m^3-year): C1: 1.05	SMRs (95% CI) for lung cancer C1: - Number of workers: 2,342 - Number of lung cancer deaths: 77 - SMR: 1.3 (1.0, 1.6) C2: - Number of workers: 1,026 - Number of lung cancer deaths: 38 - SMR: 1.4 (1.0, 2.0) C3: - Number of workers: 5,408 - Number of lung cancer deaths: 124 - SMR: 1.2 (1.0, 1.3) C4: - Number of workers: 4,027 - Number of lung cancer deaths: 85 - SMR: 1.6 (1.2, 1.98) C5:

Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

Reference	Studies in analysis	Methods and estimated exposure	Outcomes
	- C9: Steenland and Brown 1995b; United States; gold miners - C10: de Klerk and Musk 1998; Australia; gold miners	C2: 4.63 C3: 0.71 C4: 0.13 C5: 6.07 C6: 5.27 C7: 8.56 C8: 4.23 C9: 0.23 C10: 11.37 Pooled cohort: 4.27 Pooled cohort cumulative (mg/m^3-year) exposure quintiles: Q1: <0.4 Q2: 0.4–2.0 Q3: 2.0–5.4 Q4: 5.4–12.8 Q5: >12.8	- Number of workers: 9,017 - Number of lung cancer deaths: 68 - SMR: 1.1 (0.84, 1.4) C6: - Number of workers: 7,858 - Number of lung cancer deaths: 97 - SMR: 2.1 (1.7, 2.6) C7: - Number of workers: 28,481 - Number of lung cancer deaths: 135 - SMR: 0.63 (0.53, 0.75)C8: - Number of workers: 2,260 - Number of lung cancer deaths: 77 - SMR: not calculated (no comparison rates available for South Africa) C9: - Number of workers: 3,348 - Number of lung cancer deaths: 156 - SMR: 1.2 (1.0, 1.4) C10 - Number of workers: 2,213 - Number of lung cancer deaths: 135 - SMR: 1.8 (1.5, 2.1) Pooled cohort (study authors note “that there is considerable heterogeneity of results by study”): - Number of workers: 65,980 - Number of lung cancer deaths: 992 - SMR: 1.2 (1.1, 1.3) ORs (95% CI) for pooled cohort, not lagged: Q1: 1.0

Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

Reference	Studies in analysis	Methods and estimated exposure	Outcomes
			Q2: 1.0 (0.85, 1.3) Q3: 1.3 (1.1, 1.7) Q4: 1.5 (1.2, 1.9) Q5: 1.6 (1.3, 2.1) Spline curve analysis showed an exposure-related monotonic increase in risk of death due to lung cancer. ORs (95% CI) for pooled cohort, lagged by 15 years: Q1: 1.0 Q2: 1.0 (0.83, 1.3) Q3: 1.3 (1.0, 1.6) Q4: 1.5 (1.2, 1.8) Q5: 1.5 (1.2, 1.9) ORs (95% CI) for pooled cohort, miners only: Q1: 1.0 Q2: 0.9 (0.66, 1.2) Q3: 0.81 (0.59, 1.1) Q4: 1.2 (0.89, 1.6) Q5: 1.4 (1.0, 1.9) ORs (95% CI) for pooled cohort, non-miners only: Q1: 1.0 Q2: 1.2 (0.92, 1.6) Q3: 2.1 (1.6, 2.8) Q4: 1.7 (1.2, 2.4) Q5: 1.5 (0.97, 2.4) Estimated excess lifetime risk (95% CI), above background risk lifetime risk of 3–6% for death due to lung cancer, for

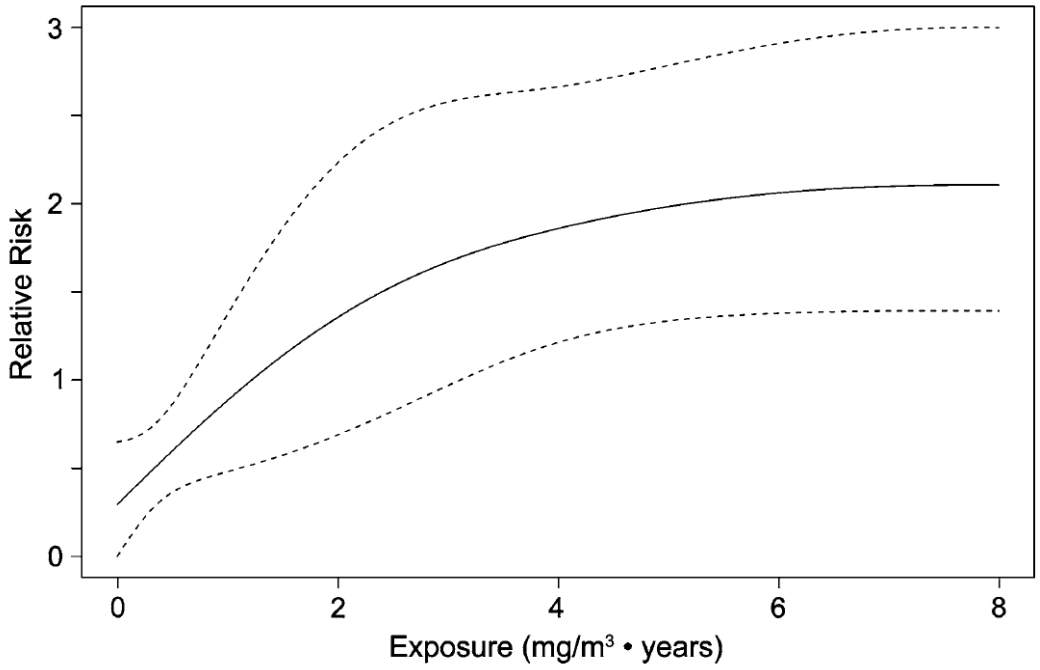
Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

Reference	Studies in analysis	Methods and estimated exposure	Outcomes
			exposure to 0.1 mg/m^3 respirable c-silica for 45 years, by location: - China: 1.1% (0.1, 2.3) - United States: 1.7% (0.2, 3.6) - Finland: 1.3% (0.1, 2.9)

[a]High number due to 1.6 million c-silica-exposed workers participating in the 1970 Finnish national census (Pukkala et al. 2005).

CI = confidence interval; OR = odds ratio; RR = risk ratio; SMR = standardized mortality ratio

Figure 2-5. Dose-Response Relationship Between Estimated Exposure to Silica and Relative Risk of Lung Cancer with its 95% Confidence Limit (No Lag Time)



Source: Lacasse et al. (2009); reproduced with permission of Kluwer Academic Publishers (Dordrecht) via Copyright Clearance Center.

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
Erren et al. 2009a, 2009b	A. Workers without silicosis Cohort studies: Armstrong et al. 1979 (Australia; miners); Puntoni et al. 1988 (Italy; refractory brick workers); Mehnert et al. 1990 (Germany; quarry workers); Amandus and Costello 1991 (United States; miners); Dong et al. 1995 (China; refractory brick workers); Finkelstein 1995 (Canada; miscellaneous industries); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (United States; diatomaceous earth workers) Case-control studies: Armstrong et al. 1979 (Australia; miners); Mastrangelo et al. 1988 (Italy; miscellaneous industries); Lagorio et al. 1990 (Italy; ceramic workers); Sherson et al. 1991 (Denmark; foundry workers) B. Workers with undefined silicosis status Cohort studies: Armstrong et al. 1979 (Australia; miners); Neuberger et al. 1986 (Austria; miscellaneous); Westerholm et al. 1986 (Sweden; miscellaneous); Finkelstein et al. 1987 (Canada; miners); Zambon et al. 1987 (Italy; miscellaneous); Puntoni et al. 1988 (Italy; refractory brick); Infante-Rivard et al. 1989 (Canada; miscellaneous); Mehnert et al. 1990 (Germany; quarry workers); Ng et al. 1990 (China; miscellaneous); Tornling et al. 1990 (Sweden; miscellaneous); Amandus and Costello 1991 (United States, miners); Amandus et al. 1991 (miscellaneous); Chen et al. 1992 (China; miscellaneous); Dong et al. 1995 (China; refractory brick workers);	Study type: meta-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis, and (B) with undefined silicosis status Literature search dates: 1966 through January 2007 Adjustments: Three studies adjusted for smoking (Dong et al. 1995; Lagorio et al. 1990; Mastrangelo et al. 1988); no smoking adjustment was made for other studies Adjustments: except for smoking, adjustments for individual studies were not reported Statistical analysis: a multi-stage strategy approach was used to examine heterogeneity between studies (fixed-effect summaries and 95% CI for various combinations of studies were calculated, with individual studies weighted by precision); homogeneity of contributing results was analyzed by χ^2 statistics; interactions with covariates was examined by meta-regression. Exposure: Not reported for overall cohort or individual studies	A. For c-silica-exposed workers without silicosis Total number of workers included in analysis: not reported Risk ratios (95% CI) for: - Entire cohort: 1.2 (1.1, 1.3) - Cohorts adjusted for smoking (three studies):1.0 (0.8, 1.3) - Cohorts not adjusted for smoking (eight studies): 1.2 (1.1, 1.4) The increased risk of 20% appears to be influenced by smoking. B. For c-silica-exposed workers with undefined silicosis status Total number of workers included in analysis: not reported Risk ratios (95% CI) for: - All studies combined: 2.1 (1.9, 2.3) - Cohort studies: 2.0 (1.7, 2.3) - Case-control studies: 2.3 (1.8, 2.9) - SIR studies: 2.6 (2.1, 3.3) - Mortality OR studies: 1.8 (1.3, 2.7) - Studies adjusted for smoking (nine studies): 2.2 (1.8, 2.7) - Studies not adjusted for smoking: 2.0 (1.8, 2.3) Homogeneity statistics indicated a substantial difference between studies,

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	Goldsmith et al. 1995 (miscellaneous); Meijers et al. 1996 (Netherlands; ceramic workers); Starzynski et al. 1996 (Poland; miscellaneous); Wang et a; 1996 (China; metal workers); de Klerk and Musk 1998 (Australia; gold miners); Checkoway et al. 1999 (United States; diatomaceous earth workers); Chan et al. 2000 (China; miscellaneous); Carta et al. 2001 (Italy; metal miners); Berry et al. 2004 (Australia; miscellaneous); Ulm et al. 2004 (Germany; quarry) Case-control studies: Steenland and Beaumont 1986 (United States; granite workers); Mastrangelo et al. 1988 (Italy; miscellaneous); Cocco et al. 1990 (Italy, miscellaneous); Lagorio et al. 1990 (Italy; miscellaneous); Hnzido et al. 1997 (South Africa; gold miners); Finkelstein 1998 (Canada; miscellaneous); Cocco et al. 2001 (China; miscellaneous); Tsuda et al. 2002 (Japan; refractory brick) SIR studies: Chia et al. 1991 (Singapore; miscellaneous); Sherson et al. 1991 (Denmark; foundry workers); Partanen et al. 1994 (Finland; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous). Mortality OR studies: Schuler et al. 1986 (Switzerland; miscellaneous); Forastiere et al. 1989 (Italy; ceramic workers)		although tests for publication bias were negative.

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
Kurihara and Wada 2004	A. Workers without silicosis Cohort studies: Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1995 (United States; dusty trade workers); Dong et al. 1995 (China; brick workers); Finkelstein 1995 (Canada; miners and other workers); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (California; diatomaceous earth miners) Case-control studies: Mastrangelo et al. 1988 (Italy; miscellaneous industries); Forastiere et al. 1986 (Italy; quarry workers; ceramic workers) B. Workers with undefined silicosis status Cohort studies: Costello and Graham 1988 (Vermont; granite workers); Guenel et al. 1989 (Denmark; stone workers); Mehnert et al. 1990 (Germany; quarry workers); Merlo et al. 1991 (Italy; brick workers); Sherson et al. 1991 (Denmark; foundry workers); Cocco et al. 1994 (Italy; miners); Costello et al. 1995 (United States; stone crushers); Dong et al. 1995 (China; brick workers); Steenland and Brown 1995b (South Dakota; gold miners); Meijers et al. 1996 (Netherlands; ceramic workers); Rafnsson and Gunnarsdottir 1997 (Iceland; diatomaceous earth workers); Cherry et al. 1998 (United Kingdom; pottery workers); de Klerk and Musk 1998 (Australia; gold miners); Checkoway et al. 1999 (California; diatomaceous earth workers); McDonald et al. 2001 (United States and	Study type: meta-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis; (B) with undefined silicosis status; (C) with silicosis; and (D) with silicosis by smoking status Literature search dates: 1966–2001 Adjustments: adjustments in individual studies included, age, sex, calendar period, race, region, smoking; individual studies may not have included all adjustments listed Statistical analysis: random effects model; publication bias assessed by funnel plot and Kendall rank correlation test; association between standardized effects and precision assessed by linear regression test intercept analysis Exposure: not reported for overall cohort or individual studies	A. Workers without silicosis Risk ratios (95% CI) for lung cancer (combined cohort and case-control studies: 0.96 (0.81, 1.15) B. Workers with undefined silicosis status Risk ratios (95% CI) for lung cancer: - Cohort studies: 1.29 (1.20, 1.40) - Case-control studies: 1.42 (1.22, 1.65) - All studies: 1.32 (1.23, 1.41) C. Workers with silicosis Risk ratios (95% CI) for lung cancer: - Cohort studies: 2.49 (2.08, 2.99) - Case-control studies: 1.89 (1.45, 2.48) - All studies: 2.37 (1.98, 2.84) D. Workers with silicosis by smoking status - Risk ratio (95% CI) for lung cancer in smokers with silicosis: 4.47 (3.17, 6.30) - Risk ratio (95% CI) for lung cancer in nonsmokers with silicosis: 2.24 (1.46, 3.43)

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	Canada; sand workers); Steenland et al. 2001a (United States; sand workers); Stern et al. 2001 (plasterers and masons) Case-control studies: Forastiere et al. 1986 (Italy; quarry workers; ceramic workers); McLaughlin et al. 1992 (China; iron-copper miners; potteries workers; tin miners; tungsten miners); De Stefani et al. 1996 (Uruguay; miscellaneous); Cherry et al. 1998 (United Kingdom; pottery and sandstone workers); Ulm et al. 1999 (Germany; ceramic workers; quarry workers); Bruske-Hofeld et al. 2000 (Germany; miscellaneous); Martin et al. 2000 (France; miscellaneous); Szadkowska-Stanczyk and Szymczak 2001 (Poland; pulp and paper workers) C. Workers with silicosis Cohort studies: Infante-Rivard et al. 1989 (Canada; miscellaneous); Ebihara et al. 1990 (Japan; miscellaneous); Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1995 (United States; dusty trade workers); Dong et al. 1995 (China; brick workers); Meijers et al. 1996 (Netherlands; ceramic workers); Brown et al. 1997 (Sweden; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous); Finkelstein 1998 (Canada; miners); Checkoway et al. 1999 (California; diatomaceous earth workers); Chan et al. 2000 (Hong Kong; miscellaneous)		

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	Case-control studies: Mehnert et al. 1990 (Germany; quarry workers); Amandus et al. 1992 (North Carolina; dusty trade workers); Dong et al. 1995 (China; brick workers); Finkelstein 1995 (Canada; miners and other workers); Meijers et al. 1996 (Netherlands; ceramic workers); Checkoway et al. 1999 (California; diatomaceous earth miners) D. Workers with silicosis by smoking status Cohort studies with silicosis based on smoking: Dong et al. 1995 (China; brick workers); Amandus et al. 1995 (United States; dusty trade workers); Ebihara et al. 1990 (Japan; miscellaneous); Ebihara and Kawami 1998 (Japan; miscellaneous); Infante-Rivard et al. 1989 (Canada; miscellaneous); Oksa et al. 1997 (Finland; miscellaneous) Case-control studies: Mastrangelo et al. 1988 (Italy; miscellaneous industries); Hnizido et al. 1997 (South Africa; gold miners)		

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
Pelucci et al. 2006	A. Workers without silicosis Cohort studies: Checkoway et al. 1999 (United States; diatomaceous earth workers); Case-control studies: Ulm et al. 1999 (Germany; stone, quarry, and ceramic workers) B. Workers with undefined silicosis status Cohort studies: Brown and Rushton 2005 (United Kingdom; industrial sand workers); Checkoway et al. 1997 (United States; diatomaceous earth workers); Checkoway et al. 1996 (United States; phosphate industry); Cherry et al. 1998 (United Kingdom; pottery refractory and sandstone workers); Chiazze et al. 1997 (United States; filament glass workers); Coggiola et al. 2003 (Italy; talc miners and millers); de Klerk and Musk 1998 (Australia; gold miners); Finkelstein and Verma 2005[a] (Canada; brick workers); Graham et al. 2004 (United States; granite workers); Kauppinen et al. 2003 (Finland; asphalt workers); McDonald et al. 2005 (United States; industrial sand workers); Merlo et al. 2004 (Italy; graphite electrode manufacturing); Moshammer and Neuberger 2004 (Austria; miscellaneous); Moulin et al. 2000 (France; stainless steel workers); Ogawa et al. 2003 (stone cutters); Pukkala et al. 2005[a] (Finland; miscellaneous); Rafnsson and Gunnarsdottir 1997 (Iceland; diatomaceous earth workers); Smailyte et al. 2004 (Lithuania; cement production);	Study type: pooled-analysis on lung cancer in c-silica-exposed workers: (A) without silicosis; (B) with undefined silicosis status; and (C) with silicosis Literature search dates: 1996–July 2005 (studies published after the IARC 1997 assessment) Adjustments: not reported for overall cohort; some adjustments reported for individual studies Statistical analysis: pooled relative risks calculated according to study design, using fixed and random effect models Exposure: not reported for overall cohort	A. Workers without silicosis Relative risks (95% CI) (random effects model) - Cohort studies: 1.19 (0.87, 1.57) - Case-control studies: 0.97 (0.68, 1.38) B. Workers with undefined silicosis status Relative risks (95% CI) (random effects model) - Cohort studies: 1.25 (1.18, 1.33) - Case-control studies: 1.41 (1.18, 1.70) C. Workers with silicosis Relative risks (95% CI) (random effects model) - Cohort studies: 1.69 (1.32, 2.16) - Case-control studies: 3.27 (1.32, 8.2) All cohort studies, for any silicosis status - Relative risk (95% CI) (random effects model): 1.34 (1.25, 1.45) - Relative risk (95% CI) (fixed effects model): 1.19 (1.16, 1.21) All case-control studies, for any silicosis status - Relative risk (95% CI) (random effects model): 1.41 (1.18, 1.67) - Relative risk (95% CI) (fixed effects model): 0.99 (0.98, 1.00) By occupational setting Cohort studies (number of cohorts) and relative risks (95% CI) - Miners (3): 1.17 (1.03, 1.32)

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	Steenland and Greenland 2004 (United States; industrial sand workers); Stone et al. 2004 (United States; fiberglass workers) Case-control studies: Bruske-Hohlfeld et al. 2000 (Germany; miscellaneous); Calvert et al. 2003 (United States; miscellaneous); Chen and Chen 2002[a] (China; tin miners); Cocco et al. 2001[a] (miners and pottery factory workers); De Stefani et al. 1996 (Uruguay; miscellaneous); Hnizdo et al. 1997[a] (South Africa; cold miners); Martin et al. 2000 (France; electricity and gas workers); Menvielle et al. 2003 (New Caledonia; miscellaneous); Rodriguez et al. 2000[a] (Spain; iron and steel foundry workers); Szadkowska-Stanczyk and Szymczak 2001 (Poland; pulp and paper workers); Tsuda et al. 2002 (China; refractory brick workers); Watkins et al. 2002[a] (United States; roofing manufacturing and asphalt production workers); Westberg and Bellander 2003[a] (Sweden; foundry workers) C. Workers with silicosis Cohort studies: Berry et al. 2004 (South New Wales; miscellaneous); Brown et al. 1997 (Sweden; miscellaneous); Carta et al. 2001 (Italy; miners and quarry workers); Chan et al. 2000 (China; miscellaneous); Checkoway et al. 1999 (United States; diatomaceous earth workers); Starzynski et al. 1996 (Poland, miscellaneous); Ulm et al. 2004 (Germany; stone and quarry workers)		- Sand workers (3) 1.29 (1.03, 1.61) - Ceramic, diatomaceous earth, and refractory brick workers (4): 1.40 (1.11, 1.75) - Miscellaneous exposure (10): 1.17 (1.12, 1.22) Case-control studies (number of cohorts) and relative risks (95% CI) - Miners (4): 1.47 (1.19, 1.82) - Sand workers (0): – - Ceramic, diatomaceous earth, and refractory brick workers (3): 1.26 (0.99, 1.62) - Miscellaneous exposure (10): 1.24 (1.02, 1.52)

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	Case-control studies: Finkelstein 1998 (Canada; miscellaneous)		
Poinen-Rughooputh et al. 2016	A. Workers classified as non-silicotic (without silicosis) Cohort studies: Chen et al.1990 (China; iron mine workers); Chen et al. 2006 (China; mine workers); Finkelstein et al.1983 (Canada; various; Mechnert et al. 1990 (Germany; quarry workers); Putoni et al. 1988 (Italy; brick workers); Sherson et 1991 (Denmark; foundry workers) Case-control studies: Lagorio et al. 1990 (Italy; ceramic workers) B. Workers classified as silicotic (with silicosis) Cohort studies: Amandus et al. 1995 (United States; miscellaneous); Berry et al.2004 (Australia; miscellaneous); Carta et al. 2001 (Sardinia; mine and quarry workers); Chan et al. 2000 (China; miscellaneous); Chen et al. 1992 (China; miscellaneous); Chen et al. 1990 (China; iron mine workers); Chen et al. 2006 (China; mine workers); Chia et al. 1991 (China; granite workers); Chiyotani et al. 1990 (Japan, miscellaneous); Finkelstein et al. 1982 (Canada; mine workers); Finkelstein 1995 (Canada; miscellaneous); Goldsmith et al. 1995 (United States: miscellaneous); Infante-Rivard et al. 1989 (Canada; miscellaneous); Marinaccio et al. 2006 (Italy; miscellaneous); Mehnert et al. 1990 (Germany; quarry workers); Merlo et al. 1995	Study type: pooled-analysis of lung cancer in c-silica-exposed workers: (A) without silicosis; (B) with silicosis Literature search dates: January 1982–April 2016 Adjustments: year of publication, presence of at least one confounding factor, smoking, industrial setting, geographical location, NOS score, person-years follow-up, number of subjects, total number of deaths Statistical analysis: pooled relative risks calculated according to study design, random effect models Cumulative silica dust exposure (mg/m^3-year) quartile ranges: >0, ≤0.83 >0.83, ≤3.9 >3.9, ≤8.35 >8.35	Workers classified as non-silicotic (without silicosis) (95% CI) (random effects model) - SMR: 1.78 (1.07, 2.96) - SIR: 1.18 (0.86, 1.62) Workers classified as silicotic (without silicosis) (95% CI) (random effects model) - SMR: 2.32 (1.91, 2.81) - SIR: 2.49 (1.87, 3.33) All studies, for any silicosis status (95% CI) (random effects model) - SMR: 1.55 (1.38, 1.75) - SIR: : 1.68 (1.45, 1.96 - PMR: 1.10 (0.89, 1.36) - MOR: 1.69 (1.26, 2.26) By occupational setting (all study types) Effect estimate (95% CI) - Miners (18): 1.48 (1.18, 1.86) - Foundry workers (4) 1.51 (1.99, 2.29) - Ceramic workers (7): 1.14 (1.05, 1.23) - Cement workers (4): 0.87 (0.42, 1.82) - Construction workers (2): 1.55 (1.31, 1.82) - Stone workers (8): 1.32 (1.15, 1.50) - Miscellaneous exposures (19): 2.03 (1.61, 2.56) By exposure (mg/m^3-year) quartile Effect estimate (95% CI)

Table 2-17. Meta- or Pooled-Analyses for Lung Cancer in c-Silica Workers Based on Silicosis Status

Reference	Studies in analysis	Estimated exposure and methods	Outcomes
	(Italy; miscellaneous); Ng et al. 1990 (China; miscellaneous); Partanen et al. 1994 (Finland; miscellaneous); Puntoni et al. 1988 (Italy; brick workers); Scarselli et al. 2011 (Italy; miscellaneous); Sherson et al. 1991 (Denmark; foundry workers); Tornling et al. 1990 (Sweden; ceramic workers); Tse et al. 2014 (China; miscellaneous); Wang et al. 1996 (China; metallurgy workers); Westerholm 1980 (Sweden; miscellaneous); Westerholm et al. 1986 (Sweden; miscellaneous); Yu et al. 2008 (China; miscellaneous); Zambon et al. 1987 (Italy; miscellaneous) Case-control studies: Forastiere et al. 1989 (Italy; miscellaneous); Fu et al. 1994 (China; tin miners); Lagorio et al. 1990 (Italy; ceramic workers); Neuberger et al. 1988 (Austria; miscellaneous); Schuller et al. 1982 (Switzerland; miscellaneous); Tsuda et al. 2002 (Japan, miscellaneous)		- Q1: 1.19 (1.02, 1.39) - Q2: 1.27 (0.89, 1.82) - Q3: 1.33 (0.94, 1.87) - Q4: 1.36 (0.87, 2.13)

[a]Studies included in analysis by occupational setting.

CI = confidence interval; IOR = incidence odds ratio; MOR = mortality odds ratio; NOS score = Newcastle-Ottawa Scale for assessing quality of nonrandomized studies in meta-analysis; OR = odds ratio; PMR = proportional mortality ratio; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Erren et al. (2009b), based on their meta-analysis of 40 studies of workers who had silicosis and 11 studies in workers without silicosis, was that the study was unable to determine if exposure to silica was associated with lung cancer in the absence of silicosis. For workers with silicosis, risk ratios and SMRs (95% CI) ranged from 1.52 (1.02, 2.26) to 4.47 (3.17, 6.30), compared to a range of 0.97 (0.69, 1.38) to 1.2 (1.0, 1.4) for workers without silicosis.

Smoking and Lung Cancer. Adjusting for potential confounding bias from smoking is important in studies examining the association between c-silica and lung cancer, because smoking is a risk factor for lung cancer (Brown 2009; Chen et al. 2007; Cox 2011; Liu et al. 2013; NIOSH 2012). Results of a nested case-control study of hard rock miners in China found that lung cancer risk associated with smoking was larger than that associated with exposure to c-silica (Chen et al. 2007) (Table 2-18). However, smoking may also interact with silica to produce lung cancer. Results of a retrospective study in China showed increased lung cancer risk in never-smokers in association with c-silica exposure and that the change in risk with increasing exposure was similar in never-smokers and ever-smokers (Table 2-18) (Liu et al. 2013). The study authors stated that "the joint effect of *[c-]*silica and smoking on lung cancer was more than additive and close to multiplicative."

Other Cancers. Cancers of the esophagus, stomach, intestine, and kidney have been reported in c-silica-exposed workers; however, associations between c-silica and these cancers have not been thoroughly studied or established (IARC 2012; NIOSH 2002). In general, findings of these studies have been inconsistent and studies often include co-exposures to other risk factors (Brown 2009). In many cases, observations of cancers other than lung were made in studies investigating the association between c-silica exposure and lung cancer, and appropriate adjustments for confounding factors were not considered (Chen and Tse 2012; NIOSH 2002).

Crystalline Silica, Oral. No studies evaluating cancer in humans or animals following oral exposure to c-silica were identified.

Amorphous Silica, Inhalation. 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.

Table 2-18. Lung Cancer Risk in Smokers and Nonsmokers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
Chen et al. 2007	Study design: case-control Industry: metal miners, pottery workers in China	Cohort: 511 lung cancer cases and 1,879 control workers from 29 mines or factories in China (100% male) employed for at least 1 year during 1972–1974, with follow-up to 1989. Cases and controls were matched to decade of birth and workplace. Methods: lung cancer mortality risk estimated from logistic regression Adjustments: smoking, cumulative exposure to arsenic and PAH; and radon (yes/no)	Exposure quintiles (Q) (mg/m^3-year): - Q1: 0.1–1.1 - Q2: 1.1–2.6 - Q3: 2.6–5.4 - Q4: 5.4–10.1 - Q5: 10.1–72.4	All facilities Effect of smoking, OR (95% CL) by pack-year tertile (T), adjusted for, arsenic, PAH, radon: T1 (0–18): 1.41 (0.96, 2.06) T2 (18–31): 2.64 (1.81, 3.84) T3 (31–180): 4.51 (3.11, 6.65) All facilities Effect of c-silica, OR (95% CL) by exposure quintile, adjusted for smoking, arsenic, PAH, radon: Q1: 1.40 (0.81,2.43) Q2: 1.54 (0.90, 2.63) Q3: 1.30 (0.75, 2.24) Q4: 1.17 (0.68, 2.06) Q5: 1.50 (0.83. 2.72) Pottery facilities Effect of c-silica, OR (95% CL) by exposure quintile, adjusted for smoking: Q1: 0.8 (0.29, 2.19) Q2: 1.3 (0.63, 2.64) Q3: 1.7 (0.82, 3.58) Q4: 1.5 (0.71, 3.21) Q5: 3.5 (1.45. 8.66) Tin mines Effect of c-silica, OR (95% CL) by exposure quintile, adjusted for smoking: Q1: 1.6 (0.75, 3.52) Q2: 1.9 (0.96, 3.78) Q3: 1.8 (0.94, 3.29) Q4: 2.1 (1.14, 3.80) Q5: 3.3 (1.66. 6.61)

Table 2-18. Lung Cancer Risk in Smokers and Nonsmokers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
				Tungsten mines Effect of c-silica, OR (95% CL) by exposure quintile, adjusted for smoking: Q1: 2.0 (0.97, 4.19) Q2: 1.4 (0.64, 2.81) Q3: 0.6 (0.32, 1.30) Q4: 0.8 (0.42, 1.51) Q5: 1.0 (0.55. 1.66) Iron-copper mines Effect of c-silica, OR (95% CL) by exposure quintile, adjusted for smoking: Q1: 1.0 (0.51, 1.77) Q2: 1.3 (0.56, 3.07) Q3: 1.8 (0.57, 5.48) Q4: NR Q5: NR
Liu et al. 2013	Study design: retrospective cohort Industry: metal miners, pottery workers in China	Cohort: 34,018 Chinese workers (86% male) not likely exposed to other lung carcinogens; employed during 1960–1974, with follow-up to 2003 Methods: To investigate the joint effect of silica and smoking, hazard ratios were estimated by crossed dichotomized silica exposure (exposed = A+, unexposed = A−) and smoking (ever smokers = B+, never smokers = B−) Adjustments: facility, sex, year of birth, smoking amount	Exposure quartiles (Q) (mg/m^3-year): - Q1: 0 - Q2: >0 - Q3: <1.12 - Q4: ≥1.12	Nonsmokers Lung cancer/nonsmokers in quartile: - Q1: 27/4960 - Q2: 50/7211 - Q3: 34/7285 - Q4: 43/4886 HRs (95% CI): - Q1: 1 - Q2: 1.10 (0.68–1.78) - Q3: 1.0 - Q4: 1.60 (1.01, 2.55) Smokers Lung cancer deaths in smokers/smokers in quartile: - Q1: 101/5430 - Q2: 368/16,417 - Q3: 199/10,850 - Q4: 270/10,997

Table 2-18. Lung Cancer Risk in Smokers and Nonsmokers Exposed to c-Silica

Reference	Study design and industry	Cohort and methods	Estimated exposure	Outcome
				HRs (95% CI) in smokers: - Q1: 2.75 (1.74, 4.35) - Q2: 3.83 (2.48, 5.90) - Q3: 3.42 (2.32, 5.05) - Q4: 5.07 (3.41, 7.52) Study authors stated that “the joint effect of *[c-]*silica and smoking was more than additive and close to multiplicative.”

CI = confidence interval; CL = confidence limit; HR = hazard ratio; NR = not reported; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon

The mortality from lung cancer was increased in workers exposed to silica (both amorphous and quartz) (SMR: 1.43; 95% CI: 1.09, 1.84) in a cohort of 2,570 diatomaceous earth workers (Checkoway et al. 1993). However, the contribution of a-silica to increased mortality is unknown, as a separate analysis for the population of workers exposed only to a-silica (n=129) was not conducted. Similarly, an increased risk for lung cancer was observed in a cohort of 231 refractory brick workers exposed to a mixture of a-silica and c-silica; however, only c-silica levels were measured (McLaughlin et al. 1997; Merget et al. 2002).

A limited number of reports from the sugarcane industry suggest a potential increased risk for lung cancer and/or mesothelioma in sugarcane farmers, although available data are inconclusive. Since sugarcane farmers are exposed to biogenic a-silica fibers (IARC 1997), this suggests a possible association between biogenic a-silica fiber exposure and lung cancer and/or mesothelioma; however, exposure levels to a-silica were not available in these studies, and sugarcane workers are also exposed to c-silica during the harvesting process when sugarcane plants are burned (Le Blond et al. 2010). A case-series report from India suggested that five observed cases of mesothelioma in sugarcane workers with no known exposure to asbestos could have been due to biogenic a-silica fiber exposure (Das et al. 1976). In a case-control study, an increased risk of lung cancer was observed in sugarcane farmers in Southern Louisiana (RR: 2.3; 95% CI: 1.8–3.0) (Rothschild and Mulvey 1982). When stratified by smoking, the association was only observed in farmers who were also smokers (OR: 2.6; 95% CI: 1.8–4.0). However, other case-control studies did not find associations between working at, or living near, a sugarcane farm and increased risk for lung cancer or mesothelioma (Brooks et al. 1992; Sinks et al. 1994).

No treatment-related tumors were reported in monkeys, rats, or guinea pigs following exposure to pyrogenic, precipitated, or gel a-silica at up to 9.9 mg/m^3 for 6 hours/day, 5 days/week for up to 18 months (Groth et al. 1981) or rats, guinea pigs, or rabbits following exposure to precipitated a-silica at 126 mg/m^3 for 8 hours/day, 7 days/week for 12–24 months (Schepers 1981).

Amorphous Silica, Oral. No studies evaluating cancer in humans following oral exposure to a-silica were identified.

In a 2-year bioassay that utilized small animal groups (18–21/sex/group per species), neoplastic lesions attributable to dietary exposure to a-silica gel exposure were not observed at doses up to 2,010 mg/kg/day in F344 rats or doses up to 6,010 in B6C3F1 mice (Takizawa et al. 1988). In another study, neoplastic lesions attributable to dietary exposure to pyrogenic a-silica were not observed in Wistar rats exposed to

100 mg/kg/day for 24 months, compared with historical controls (concurrent controls were not evaluated) (Lewinson et al. 1994). However, the reliability of this study is low because it utilized small animal groups (20/sex/group), lacked a concurrent control, and used a single dose level that did not approach the maximum tolerable dose (MTD) (e.g., no systemic toxicity was observed).

2.19 GENOTOXICITY

Crystalline Silica. Available evidence indicates that c-silica is a genotoxic agent in mammalian cells, with the ability to cause mutagenicity, clastogenicity, and DNA damage. Results of *in vivo* human studies, *in vivo* animal studies, and *in vitro* studies evaluating the genotoxicity of c-silica are summarized below and in Tables 2-19, 2-20, and 2-21, respectively.

Table 2-19. Genotoxicity of c-Silica in Occupational Studies

Exposure group	Silica species	End point	Results	Reference
Patients diagnosed with lung cancer and silicosis[a]	c-Silica (not specified)	Gene mutation frequency of p53 gene	+	Liu et al. 2000
Foundry and pottery workers[b]	Quartz	DNA strand breaks in peripheral lymphocytes	+	Basaran et al. 2003
Stone crushers[b]	c-Silica (not specified)	Chromosomal aberrations in peripheral whole-blood samples	+	Sobti and Bhardwaj 1991
Stone crushers[b]	c-Silica (not specified)	Sister chromatid exchanges in peripheral whole-blood samples	+	Sobti and Bhardwaj 1991
Marble factory and stone quarry workers[b]	c-silica (not specified)	DNA adducts in nasal epithelial cells	+	Peluso et al. 2015
Glass industry workers, sand blasters, and stone grinders[c]	c-Silica (not specified)	Micronuclei in peripheral lymphocytes	+	Demircigil et al. 2010
Glass industry workers, sand blasters, and stone grinders[c]	c-Silica (not specified)	Micronuclei in nasal epithelial cells	+	Demircigil et al. 2010

[a]Diagnosis of silicosis as a proxy for c-silica exposure.
[b]It was not reported whether or not exposed workers had silicosis.
[c]Silicosis was diagnosed in 50% of former workers (n=10) and 24% of current workers (n=40); micronuclei were increased in both current and former worker populations.

+ = positive result; DNA = deoxyribonucleic acid

Table 2-20. Genotoxicity of c-Silica *In Vivo* Animal Studies

Species	Silica species	End point	Results	Reference
Rat (inhalation)	Cristobalite	Gene mutation at *hprt* locus in alveolar type II epithelial cells	+	Johnston et al. 2000
Rat (intratracheal)	Quartz	Gene mutation at *hprt* locus in alveolar type II epithelial cells	+	Driscoll et al. 1997
Rat (intratracheal)	Quartz	DNA strand breaks in lung epithelial cells	+	Knaapen et al. 2002
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001a
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001b
Rat (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	+	Seiler et al. 2001c
Hamster (intratracheal)	Quartz	8-OHdG modified DNA in alveolar cells	–	Seiler et al. 2001c

+ = positive result; – = negative result; 8-OHdG = 8-hydroxydeoxyguanosine; DNA = deoxyribonucleic acid

Table 2-21. Genotoxicity of c-Silica *In Vitro*

			Results		
Species (test system)	Silica species	End point	With activation	Without activation	Reference
Prokaryotic organisms:					
Bacillus subtilis (H17 Rec$^+$, M45 Rec$^-$)	c-Silica (not specified)	DNA repair	NT	–	Kada et al. 1980
B. subtilis (H17 Rec$^+$, M45 Rec$^-$)	c-Silica (not specified)	DNA repair	NT	–	Kanematsu et al. 1980
Mammalian cells:					
RLE-6TN rat alveolar epithelial cells	BAL cells from quartz-exposed rats[a]	Mutation at *hprt* locus	NT	+	Driscoll et al. 1997
Muta^{TM}Mouse lung epithelial cells	Quartz	*cII* and *lacZ* mutant frequency	NT	–	Jacobsen et al. 2007
Human small airway epithelial cells	Quartz	DNA strand breaks	NT	+	Msiska et al. 2010
16HBE bronchial epithelial cells	Quartz	DNA strand breaks	NT	+	Zheng et al. 2017
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Msiska et al. 2010
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Fanizza et al. 2007
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Cakmak et al. 2004
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002a

Table 2-21. Genotoxicity of c-Silica *In Vitro*

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
A549 human bronchial epithelial cancer cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002b
Hel 299 human embryonic lung cells	Quartz	DNA strand breaks	NT	+	Zhong et al. 1997b
RLE-6TN rat alveolar epithelial cells	Quartz	DNA strand breaks	NT	+	Li et al. 2007
RLE-6TN rat alveolar epithelial cells	Quartz	DNA strand breaks	NT	+	Schins et al. 2002b
Rat alveolar macrophages	c-Silica (not specified)	DNA strand breaks	NT	+	Zhang et al. 2000
Rat alveolar macrophages	c-Silica (not specified)	DNA strand breaks	NT	+	Zhang et al. 1999
Muta^{TM}Mouse lung epithelial cells	Quartz	DNA strand breaks	NT	–	Jacobsen et al. 2007
V79 Chinese hamster lung fibroblasts	Quartz	DNA strand breaks	NT	+	Zhong et al. 1997b
Muta^{TM}Mouse lung epithelial cells	Quartz	Oxidative DNA damage	NT	±	Jacobsen et al. 2007
A549 human bronchial epithelial cancer cells	Quartz	8-OHdG modified DNA	NT	+	Schins et al. 2002a
RLE-6TN rat alveolar epithelial cells	Quartz	8-OHdG modified DNA	NT	+	Li et al. 2007
RLE-6TN rat alveolar epithelial cells[a]	Quartz	8-OHdG modified DNA	NT	+	Schins et al. 2002a
Hel 299 human embryonic lung cells	Quartz	Chromosomal aberrations	NT	–	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Chromosomal aberrations	NT	–	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Chromosomal aberrations	NT	–	Price-Jones et al. 1980
SHE cells	Quartz	Chromosomal aberrations	NT	+	Elias et al. 2006
SHE cells	Quartz	Chromosomal aberrations	NT	–	Oshimura et al. 1984
SHE cells	Diatomaceous earth (~50% cristobalite)	Chromosomal aberrations	NT	+	Elias et al. 2006
Hel 299 human embryonic lung cells	Quartz	Micronuclei	NT	+	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Zhong et al. 1997a
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Liu et al. 1996b

Table 2-21. Genotoxicity of c-Silica *In Vitro*

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	+	Nagalakshmi et al. 1995
V79 Chinese hamster lung fibroblasts	Quartz	Micronuclei	NT	–	Price-Jones et al. 1980
CHO cells	Quartz	Micronuclei	NT	+	Hart and Hesterberg 1998
CHO cells	Cristobalite	Micronuclei	NT	+	Hart and Hesterberg 1998
CHO cells	Diatomaceous earth (42% c-silica)	Micronuclei	NT	+	Hart and Hesterberg 1998
SHE cells	Quartz	Micronuclei	NT	–	Oshimura et al. 1984
Human peripheral lymphocytes and monocytes	Quartz	Sister chromatid exchanges	NT	±	Pairon et al. 1990
Human peripheral lymphocytes	Quartz	Sister chromatid exchanges	NT	–	Pairon et al. 1990
Human peripheral lymphocytes and monocytes	Tridymite	Sister chromatid exchanges	NT	+	Pairon et al. 1990
Human peripheral lymphocytes	Tridymite	Sister chromatid exchanges	NT	–	Pairon et al. 1990
BALB/3T3 mouse embryo cells	Quartz	Cell transformation	NT	+	Keshava et al. 1999
SHE cells	Quartz	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Quartz	Cell transformation	NT	+	Elias et al. 2006
SHE cells	Quartz	Cell transformation	NT	+	Hesterberg and Barret 1984
SHE cells	Quartz	Cell transformation	NT	–	Oshimura et al. 1984
SHE cells	Cristobalite	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (>50% c-silica)	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (~50% c-silica)	Cell transformation	NT	+	Elias et al. 2006

Table 2-21. Genotoxicity of c-Silica *In Vitro*

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
Isolated DNA					
Herring sperm genomic DNA	Quartz	DNA damage	NT	+	Daniel et al. 1993
λHindIII-digested DNA	Quartz	DNA damage	NT	+	Shi et al. 1994
λHindIII-digested DNA	Quartz	DNA damage	NT	+	Daniel et al. 1993
λHindIII-digested DNA	Quartz	DNA damage	NT	+	Daniel et al. 1995
λHindIII-digested DNA	Tridymite	DNA damage	NT	+	Daniel et al. 1995
λHindIII-digested DNA	Cristobalite	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Quartz	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Tridymite	DNA damage	NT	+	Daniel et al. 1995
PM2 supercoiled DNA	Cristobalite	DNA damage	NT	+	Daniel et al. 1995
Calf thymus DNA	Quartz	DNA binding	NT	+	Mao et al. 1994

[a]RLE-6TN cells were incubated with BAL cells collected from rat lungs 15 months after a single intratracheal exposure to 10 or 100 mg/kg of α-quartz.

+ = positive result; - = negative result; ± = marginal result; 8-OHdG = 8-hydroxydeoxyguanosine; BAL = bronchoalveolar lavage; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NT = not tested; SHE = Syrain hamster embryo

Human Occupational Studies. Chromosomal and DNA damage have been reported in a limited number of studies evaluating workers with occupational exposure to c-silica.

DNA strand breaks were significantly increased ($p<0.001$) in peripheral lymphocytes from a cohort of foundry and pottery workers exposed to c-silica for an average of 14–15 years, compared with unexposed referents (Basaran et al. 2003). The mean occupational exposure levels to respirable dust and respirable quartz in foundry workers were 16.7±1.01 and 0.72±0.35 mg/m^3, respectively; exposure levels were not reported for pottery workers (et Basaran al. 2003). The prevalence of 3-(2-deoxy-β-D-erythro-pentafuranosyl)pyrimido[1,2-α]purin-10(3H)-one-deoxyguanosine adducts was increased in the nasal epithelium of marble factory and stone quarry workers exposed to c-silica; exposure levels were not reported (Peluso et al. 2015).

Chromosomal aberrations and sister chromatid exchanges were significantly increased ($p<0.01$) by 1.5–2-fold in whole-blood samples (cell types not specified) from a cohort of stone crushers exposed to c-silica, compared with unexposed referents (Sobti and Bhardwaj 1991). Findings remained significant when workers were stratified by alcohol use and smoking status. Exposure levels and duration of

exposure were not reported. Micronuclei frequency was significantly ($p<0.001$) increased by 2–3-fold in peripheral lymphocytes and nasal epithelial cells from a cohort of glass industry workers, sand blasters, and stone grinders exposed to c-silica for an average of 7 years, compared with unexposed referents (Demircigil et al. 2010). The cumulative exposure to c-silica was significantly associated with micronuclei frequencies in both cell types (regression coefficient [95% CI] = 6.71 [5.06–8.37] for peripheral lymphocytes and 5.47 [4.56–6.37] for nasal epithelial cells; $p<0.001$); however, cumulative exposure levels were not reported (Demircigil et al. 2010).

Animal Studies. Evidence from a limited number of animal studies indicates that c-silica is a mutagenic and DNA damaging agent *in vivo*; however, the susceptibility appears to differ between species, with effects observed in rats but not hamsters.

The number of mutations at the *hprt* locus was significantly increased ($p<0.05$) in alveolar type II epithelial cells isolated from rat lungs following exposure to cristobalite via inhalation at concentrations of 3 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks (Johnston et al. 2000). Similarly, the number of gene mutations at the *hprt* locus was significantly increased ($p<0.05$) in a dose-related manner in alveolar type II epithelial cells isolated from rat lungs 15 months after a single intratracheal instillation of 10 or 100 mg/kg of quartz, compared with controls (Driscoll et al. 1997).

DNA strand breaks were significantly increased ($p<0.05$) in lung epithelial cells isolated from rats 3 days after a single intratracheal instillation of 2 mg/rat (9 mg/kg, based on reported body weights) of quartz, compared with controls (Knaapen et al. 2002). When the quartz samples were pretreated with the surface modifying compounds, polyvinylpyridine-*N*-oxide or aluminum lactate, DNA damage was inhibited, suggesting a critical role of the reactive particle surface in quartz-induced DNA damage *in vivo*. 8-Hydroxydeoxyguanosine (8-OHdG) modified DNA was increased in a time- and dose-dependent manner in alveolar cells isolated from rat lungs 3, 21, or 90 days after a single intratracheal instillation of quartz at doses ≥1.2 mg/rat (6 mg/kg, based on reported body weights), indicating oxidative DNA damage; modified DNA was not significantly elevated at doses ≤0.6 mg/rat (3 mg/kg, based on reported body weights) (Seiler et al. 2001a, 2001b, 2001c). However, 8-OHdG modified DNA was not significantly elevated in alveolar cells isolated from hamster lungs 90 days after a single intratracheal instillation of quartz at doses up to 12 mg/kg (Seiler et al. 2001c).

In vitro Studies. Evidence from the numerous *in vitro* studies provides consistent evidence that c-silica is a DNA damaging agent. Evidence also suggests that c-silica is mutagenic and clastogenic; however, there are some inconsistencies in the results between different test systems.

The number of gene mutations at the *hprt* locus was significantly increased in rat alveolar epithelial cells incubated with bronchoalveolar lavage cells collected from rat lungs 15 months after a single intratracheal instillation of quartz particles at a dose of 10 or 100 mg/kg; mutations were significantly increased in a dose-related manner when the bronchoalveolar lavage cell:epithelial cell ratio was 50:1, but not 10:1 (Driscoll et al. 1997). However, *cII* and *lacZ* mutant frequencies were not elevated in Muta^{TM}Mouse lung epithelial cells exposed to quartz particles *in vitro* (Jacobsen et al. 2007).

DNA repair was not induced in the Rec-assay in *Bacillus subtilis* (Kada et al. 1980; Kanematsu et al. 1980). However, DNA strand breaks and/or 8-OHdG modified DNA were consistently observed in various human, rat, and hamster lung cell lines exposed to quartz particles *in vitro* (Cakmak et al. 2004; Fanizza et al. 2007; Li et al. 2007; Msiska et al. 2010; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000; Zhong et al. 1997b). Oxidative DNA damage was reported as "marginally" increased ($p=0.05$) in Muta^{TM}Mouse lung epithelial cells exposed to quartz particles *in vitro*, compared with control; however, the number of DNA strand breaks was not significantly increased following quartz exposure (Jacobsen et al. 2007). Generation of reactive oxygen species (ROS) following c-silica exposure was associated with DNA damage in several of these studies (Li et al. 2007; Msiska et al. 2010; Schins et al. 2002a, 2002b; Zhang et al. 1999, 2000), and surface modifications of quartz that decrease hydroxyl-radical generation and reduce cell uptake led to reductions in quartz-mediated DNA damage (Schins et al. 2002a). In various isolated DNA samples, DNA damage was consistently observed following incubation with c-silica (quartz, tridymite, cristobalite) (Daniel et al. 1993, 1995; Shi et al. 1994) and DNA binding to c-silica particles was observed (Mao et al. 1994).

Available data indicate that c-silica can cause clastogenic effects; however, evidence is not conclusive. Both chromosomal aberrations and cytotoxicity were significantly increased in Syrian hamster embryo (SHE) cells following *in vitro* exposure to quartz and calcined diatomaceous earth (approximately 50% crystallization) (Elias et al. 2006). Chromosomal aberrations were not observed in SHE cells at lower, non-cytotoxic concentrations of quartz (Oshimura et al. 1984). Additionally, chromosomal aberrations were not induced in human embryonic lung cells or Chinese hamster lung fibroblasts following *in vitro* exposure to quartz (Nagalakshmi et al. 1995; Price-Jones et al. 1980). In contrast, several studies reported micronuclei induction following exposure to quartz or calcined diatomaceous earth in various cell lines,

including human embryonic lung cells, Chinese hamster fibroblasts, and Chinese hamster ovary (CHO) cells (Hart and Hesterberg 1998; Nagalakshmi et al. 1995; Zhong et al. 1997a). Low concentrations of quartz did not induce micronuclei in Chinese hamster fibroblasts or SHE cells (Oshimura et al. 1984; Price-Jones et al. 1980). Sister chromatid exchanges were induced in mixed human peripheral lymphocyte and monocyte cultures following exposure to tridymite at cytotoxic concentrations, but results with quartz were inconclusive (only significant in 1/3 replicates at cytotoxic concentration); neither tridymite nor quartz induced sister chromatid exchanges in purified human peripheral lymphocyte cultures (Pairon et al. 1990).

Quartz induced cell transformation in mouse embryo cells, and transformed cells showed significant genomic instability compared with non-transformed cells (Keshava et al. 1999). Cell transformation and cytotoxicity were induced in a concentration-related manner in SHE cells following exposure to various crystalline species, including quartz, cristobalite, and heated diatomaceous earth samples with some crystallization (Elias et al. 2000, 2006; Hesterberg and Barret 1984). The extent of cytotoxicity of various c-silica samples and the induction of cell transformation was not correlated; however, transforming potency was well-correlated with the amount of hydroxyl radicals generated (Elias et al. 2000, 2006). Cell transformation was not observed in SHE cells at lower, noncytotoxic concentrations of quartz (Oshimura et al. 1984).

Amorphous Silica. a-Silica has been shown to cause DNA damage and chromosomal aberrations *in vitro*; however, concentrations producing these effects are approximately 2–4-fold higher than c-silica under similar experimental conditions. The *in vivo* database is too limited to draw conclusions. *In vivo* and *in vitro* genotoxicity studies evaluating a-silica are summarized in Table 2-22.

Table 2-22. Genotoxicity of a-Silica

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
In vivo					
Rat (inhalation)	Precipitated a-silica	Gene mutation at *hprt* locus in alveolar type II epithelial cells		–	Johnston et al. 2000
Mouse (oral)	Silicon dioxide (NS)	Micronuclei in peripheral erythrocytes		–	Morita et al. 1997
Mouse (intraperitoneal)	Silicon dioxide (NS)	Micronuclei in peripheral erythrocytes		–	Morita et al. 1997

Table 2-22. Genotoxicity of a-Silica

Species (test system)	Silica species	End point	Results		Reference
			With activation	Without activation	
In vitro					
Mammalian cells:					
A549 human lung epithelial cells	Colloidal a-silica	DNA strand breaks	NT	±	Guidi et al. 2013
Hel 299 human embryonic lung cells	a-Silica gel	DNA strand breaks	NT	+	Zhong et al. 1997b
RAW264.7 murine macrophages	a-Silica gel	DNA strand breaks	NT	+	Guidi et al. 2013
V79 Chinese hamster lung fibroblasts	a-Silica gel	DNA strand breaks	NT	+	Zhong et al. 1997b
SHE cells	Diatomaceous earth (0% c-silica)	Chromosomal aberrations	NT	+	Elias et al. 2006
SHE cells	Diatomaceous earth (<1.5% c-silica)	Chromosomal aberrations	NT	+	Elias et al. 2006
SHE cells	Vitreous a-silica	Chromosomal aberrations	NT	+	Elias et al. 2006
A549 human lung epithelial cells	Colloidal a-silica	Micronuclei	NT	–	Guidi et al. 2013
RAW264.7 murine macrophages	Colloidal a-silica	Micronuclei	NT	+	Guidi et al. 2013
V79 Chinese hamster lung fibroblasts	a-Silica gel	Micronuclei	NT	+	Liu et al. 1996b
CHO cells	Diatomaceous earth (4% crystalline)	Micronuclei	NT	+	Hart and Hesterberg 1998
SHE cells	Diatomaceous earth (≤6% c-silica)	Cell transformation	NT	+	Elias et al. 2000
SHE cells	Diatomaceous earth (<1.5% c-silica)	Cell transformation	NT	+	Elias et al. 2006
SHE cells	Diatomaceous earth (0% c-silica)	Cell transformation	NT	–	Elias et al. 2006
SHE cells	Pyrogenic a-silica	Cell transformation	NT	–	Elias et al. 2000
SHE cells	Vitreous a-silica	Cell transformation	NT	–	Elias et al. 2006

+ = positive result; - = negative result; ± = inconclusive result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NS = not specified; NT = not tested; SHE = Syrain hamster embryo

Animal Studies. No significant increases in the number of mutations at the *hprt* locus were observed in alveolar type II epithelial cells isolated from rat lungs following exposure to precipitated a-silica via inhalation at concentrations of 50 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks (Johnston et al. 2000). As discussed above, exposure to c-silica under the same conditions resulted in a significant increase in mutations. The only other available *in vivo* study showed no induction of micronuclei in peripheral blood erythrocytes from mice following oral or intraperitoneal exposure to silicon dioxide at doses up to 5,000 mg/kg (Morita et al. 1997).

In vitro Studies. Available evidence from *in vitro* studies show that a-silica is capable of causing DNA and chromosomal damage at concentrations 2–4-fold higher than c-silica; however, findings are inconsistent between studies. DNA strand breaks were significantly elevated in human embryonic lung cells and Chinese hamster lung fibroblasts following exposure to a-silica gel *in vitro*; however, the concentration of a-silica gel required to induce micronuclei was 4-fold higher than the concentration of c-silica (quartz) required to induce micronuclei under the same experimental conditions (Zhong et al. 1997b). Some evidence of DNA strand breaks was observed in human lung epithelial cells exposed to colloidal a-silica at noncytotoxic concentrations up to 80 µg/mL; however, the results did not exhibit concentration-dependence (Guidi et al. 2013). In murine macrophage cells, DNA strand breaks were only observed at colloidal a-silica particle concentrations that caused cytotoxicity (≥5 µg/mL) (Guidi et al. 2013).

Both chromosomal aberrations and cytotoxicity were significantly increased in exposures to natural, non-crystalline diatomaceous earth; however, exposure to vitreous a-silica did not induce chromosomal aberrations (Elias et al. 2006). a-Silica did not induce micronuclei in human lung epithelial cells; however, colloidal a-silica, a-silica gel, and non-crystalline diatomaceous earth induced micronuclei in murine macrophage cells, Chinese hamster lung fibroblasts, and CHO cells, respectively (Guidi et al. 2013; Hart and Hesterberg 1998; Liu et al. 1996b). The concentration of a-silica required to induce micronuclei was 2-fold higher than the concentration of quartz required to induce micronuclei in Chinese hamster lung fibroblasts (Liu et al. 1996b).

Both cell transformation and cytotoxicity were induced in a concentration-related manner in SHE cells exposed to natural diatomaceous earth samples with minimal (up to 6%) crystallization (Elias et al. 2000, 2006). However, neither cell transformation nor cytotoxicity was observed in SHE cells exposed to unheated diatomaceous earth samples (0% crystallization) or pyrogenic or vitreous a-silica samples (Elias et al. 2000, 2006).

2.20 MECHANISMS OF ACTION

2.20.1 Pharmacokinetic Mechanisms

Absorption. Several mechanisms contribute to the absorption of inhaled particles: (1) physical transformation of particles deposited in the lung, including fragmentation or surface modification; (2) dissolution of particles; and (3) phagocytosis of particles by macrophages (Bailey et al. 2007; ICRP 1994).

The relative contributions of these mechanisms appear to depend on several factors, including: (1) particle size of the inhaled aerosol; (2) water solubility; and (3) surface characteristics of the particles that affect macrophage activation and cytotoxicity. Macrophage phagocytosis and migration is by far the dominant mechanism for absorption of silica particles from the pulmonary region of the respiratory tract.

Phagocytosis of silica particles is mediated by interactions with cell membrane receptors (Hamilton et al. 2008). Following uptake, silica particles trigger cytotoxicity and apoptosis (Hamilton et al. 2008; Hornung et al. 2008; Thibodeau et al. 2004), leading to impaired particle clearance (Donaldson and Borm 1998; Fenoglio et al. 2000). Because of the effect of cytotoxicity on macrophage-mediated clearance, physical characteristics of silica particles that affect cytotoxic potential may contribute to differences in lung clearance of silica particles (Begin et al. 1987; Brown and Donaldson 1996; Fenoglio et al. 2000).

Dissolution, which contributes to absorptive clearance of some types of particles, is negligible for c-silica because of the low solubility of c-silica particles. Dissolution may play a larger role in clearance of a-silica, and may contribute to its faster clearance compared to c-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981).

Studies conducted in Caco-2 cell culture monolayers, a differentiated cell line derived from human small intestine, have found that amorphous silica particles 50–200 nm in diameter agglomerate in gastrointestinal fluids (Sakai-Kato et al. 2014). Absorptive transfer across the monolayers was negligible when the monolayers were exposed to silica particles >100 nm.

Distribution. Based on observations of silica particles in mediastinal lymph nodes following inhalation, lymph may provide a mechanism for system distribution of silica particles (Absher et al. 1992; Vacek et al. 1991).

Metabolism. Absorbed silica is not metabolized. Although silica particles are highly insoluble, *in vitro* studies have found that silica particles dissolved from slate dust can bind to serum albumin (Singh et al. 1984).

Excretion. Renal handling of silicon has been studied in clinical studies of healthy adults and in chronic renal failure patients (Alder and Berlyne 1986; Berlyne and Alder 1986). In these studies, silicon was measured in urine and plasma using atomic absorption spectrophotometry, which could not distinguish chemical forms of silicon. The exposure source of the silicon in plasma and urine was not known and exposure may have been to metallic silicon or silicate. Urinary excretion of silicon was correlated with urinary calcium, suggesting that it may be excreted as an orthosilicate complex (Alder and Berlyne 1986; Berlyne and Alder 1986). Clearance studies showed that mechanisms of urinary excretion of silicon involve glomerular filtration and renal tubular secretion (Alder and Berlyne 1986; Berlyne and Alder 1986).

2.20.2 Mechanisms of Toxicity

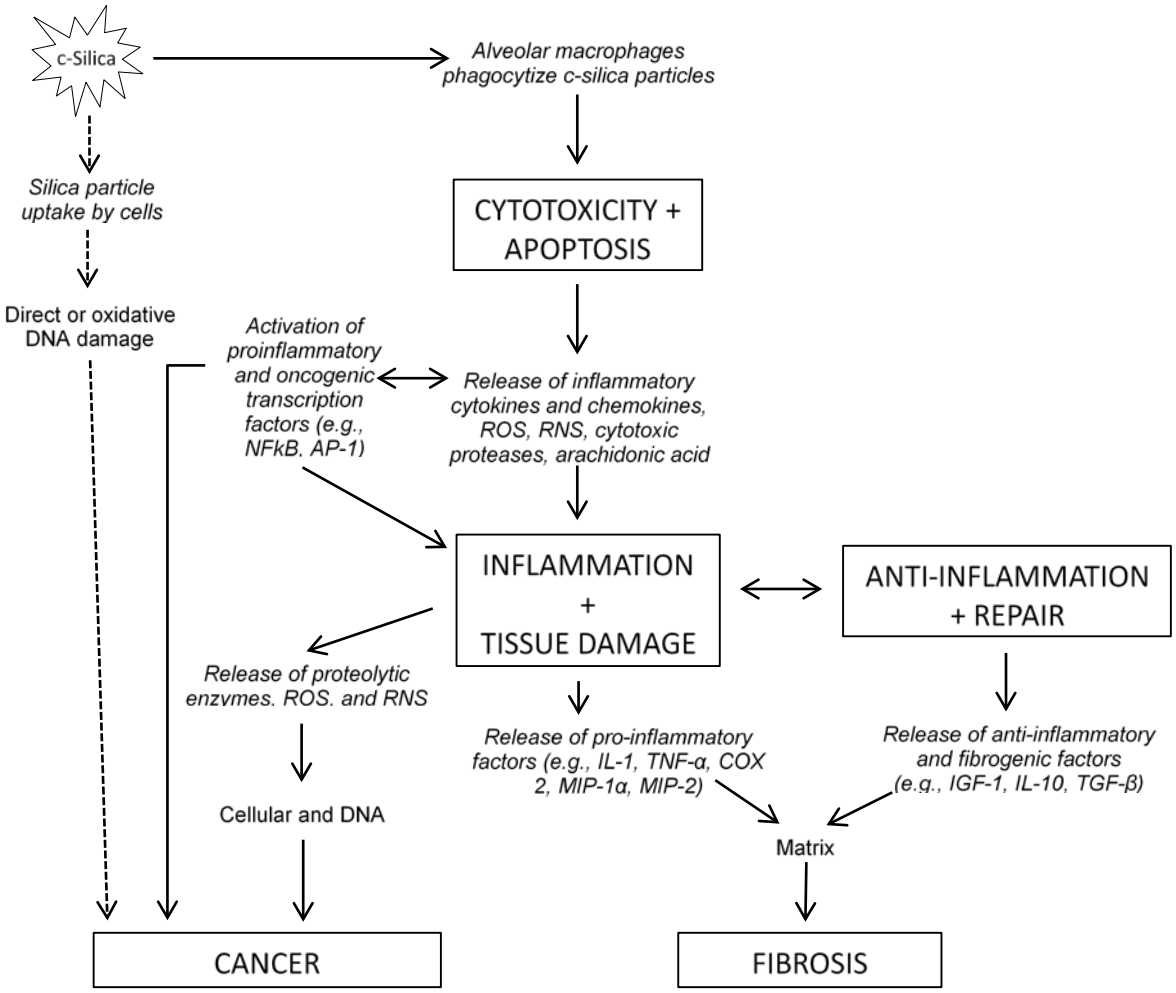
The mechanisms of toxicity for the main health effects of concern, including silicosis, COPD, lung cancer, autoimmune disease, and renal disease, for c-silica are discussed below.

Role of Crystalline Silica Surface and Structural Features. The ability of different c-silicas (tridymite, cristobalite, and quartz) to induce fibrosis can vary. In addition, c-silica is more fibrogenic than a-silica. 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; Turci et al. 2016). Freshly fractured c-silica particles (i.e., particles generated during abrasive blasting) are much more cytotoxic than “aged” particles due to the abundance of free radicals on the fresh surface (silanol groups, ionized silanol groups). This increased redox potential leads to increased inflammatory reactions in the lungs. Processing of particles (through heating, grinding, chemical treatment, etc.) can decrease surface reactivity of c-silica. c-Silica particles can

readily adsorb other dusts and minerals, which may alter biological activity. Furthermore, the surface density of silanol, which varies between polymorphs, affects *in vitro* biological activity of silica (Murashov et al. 2006). Particle size also is likely to affect toxicity, although the relationship between c-silica particle size and biological activity is still unclear. Studies have come to divergent conclusions, with some suggesting that particles in the 1–2-µm size range are the most fibrogenic, while others indicate that larger particles (≥5 µm) have the greatest fibrogenic potential. Therefore, exposure conditions, including differences in dust composition, surface reactivity, particle size, and particle age, can alter the exposure-response relationship between c-silica and disease, particularly silicosis, and potentially trigger various response mechanisms.

Silicosis. Lung injury is a well-known effect of c-silica exposure (see Respiratory Effects in Section 2.4), and the general mechanisms of silicosis have been extensively investigated (reviewed by Cassel et al. 2008; Chen and Shi 2002; Cox 2011; Ding et al. 2002; Franklin et al. 2016; Fujimura 2000; Huaux 2007; IARC 2012; Kawasaki (2015); Leung et al. 2012; Mossman and Churg 1998; Mossman and Glen 2013; Parks et al. 1999; Pollard 2016; Rimal et al. 2005; Shi et al. 2001; Tsugita et al. 2017; Weissman et al. 1996). The underlying mechanism of silicosis is considered to be an inflammatory process (see Figure 2-6). In the lung, inhaled c-silica particles are phagocytized by alveolar macrophages. Phagocytosis appears to involve scavenger recognition receptors (e.g., SR-B1) (Tsugita et al. 2017). Release of phagosomal contents triggers activation of NALP3 and inflammasome activation leading to release of a wide array of inflammatory cytokines and chemokines (notably TNF-α and IL-1, capsase-1), ROS and reactive nitrogen species (RNS), and arachidonic acid metabolites (Abderrazak et al. 2015; Cassel et al. 2008; Latz 2010; Pollard 2016; Sayan and Mossman 2016; Tsugita et al. 2017; Varela et al. 2017). These chemicals damage nearby cells and the extracellular matrix and also recruit additional macrophages to the site of damage. Additionally, various transcription factors, notably the pro-inflammatory and oncogenic factors nuclear factor kappa-B (NF_kB) and activator protein (AP-1), are upregulated during this inflammatory response, potentially via reactive species or proteolytic pathways. This recurring cycle of macrophage phagocytosis, death, and release of intracellular contents results in a chronic inflammatory process (alveolitis). Injury to other pulmonary cells (e.g., epithelial cells and fibroblasts) resulting from interactions with c-silica particles may also contribute to alveolitis. However, studies in animal models indicate that apoptosis of macrophages, and subsequent influx of additional macrophages, is the predominant mediator of alveolitis. The inflammatory phase is followed by a reparative phase, which leads to release of anti-inflammatory and fibrogenic factors (e.g., EGF, IGF-1, IL-10, TGF-β) to stimulate recruitment and proliferation of mesenchymal cells, leading to tissue repair and remodeling. Additionally, chronic inflammation damages alveolar type I epithelial cells, which

Figure 2-6. Overview of the Major Biological Processes Proposed to Underlie the Pathogenesis of Silicosis and Lung Cancer



Inhaled c-silica is phagocytized by alveolar macrophages. The phagocytized c-silica causes cytotoxicity and apoptosis, leading to release of intracellular c-silica as well as several chemicals (inflammatory cytokines and chemokines, ROS, and arachidonic acid metabolites). These chemicals damage nearby cells and extracellular matrix, activate transcription factors, and recruit additional macrophages to the site of damage. This cycle repeats, causing a chronic inflammatory process. The inflammatory phase is followed by a reparative phase, which leads to release of anti-inflammatory and fibrogenic factors to stimulate tissue repair and remodeling. Excessive cycling between the inflammatory and reparative phases leads to excess extracellular matrix deposition, ultimately leading to fibrosis. The inflammatory process can also lead to release of proteolytic enzymes and oxidants that cause cellular and DNA damage, resulting in genotoxic events that can trigger a carcinogenic process. This secondary, inflammation-driven genotoxicity pathway is the most likely mechanism underlying c-silica-induced cancer; however, a direct genotoxic effect of c-silica particles cannot be ruled out (see dashed arrows).

DNA = deoxyribonucleic acid; RNS= reactive nitrogen species; ROS = reactive oxygen species

Sources: Borm et al. (2011); Chen and Shi (2002); Cox (2011); Ding et al. (2002); Fujimura (2000); Huaux (2007); IARC (2012); Leung et al. (2012); Mossman and Chung (1998); Mossman and Glenn (2013); Rimal et al. (2005); Schins (2002a); Shi et al. (2001); Weissman et al. (1996)

triggers hyperplasia and hypertrophy of type II epithelial cells, which also leads to tissue repair and remodeling. An *in vitro* study in human lung epithelial cells indicates that c-silica increases expression of several genes involved in immune and inflammatory pathways (Chan et al. 2017). Persistent cycling between the inflammatory and reparative phases leads to excess extracellular matrix deposition, ultimately leading to fibrosis. Micro RNA-regulated increases in extracellular matrix protein levels is associated with decreased lung function in c-silica workers (Rong et al. 2018). The inflammatory cytokines TNF-α and IL-1 appear to be critical in the fibrotic process, as these cytokines are required for the development of c-silica-induced fibrosis in animal models, and individuals with certain TNF-α or IL-1 polymorphisms show an increased risk of developing silicosis (see Section 3.2, Children and Other Populations That Are Unusually Susceptible, for more details). While the major biological processes underlying silicosis have been established and the role of surface and structural properties have been acknowledged, the molecular events mediating the inflammatory response in alveolar macrophages have not been fully elucidated (reviewed by Chen and Shi 2002; Cox 2011; Ding et al. 2002; Huaux 2007; Leung et al. 2012; Mossman and Glenn 2013; Shi et al. 2001). A sequence of events that could potentially lead to the induction of inflammation after phagocytosis of c-silica by macrophages includes: (1) cellular uptake of c-silica into a phagosome via the scavenger receptor MARCO; (2) swelling of phagosome, followed by lysing of phagosome and release of contents into cytosolic compartment; (3) activation of nucleotide-binding domain, leucine-rich repeat protein NALP3; (4) association of NALP3 with intracellular adapter protein ASC and pro-caspase-1, forming the NALP3 inflammasome; (5) activation of caspase-1 by inflammasome, leading to activation of proinflammatory interleukins (e.g., IL-1β, IL-18) that were upregulated by activation of NF_kB via an unknown mechanism; and (6) activation of downstream mediators of inflammation, such as tumor necrosis factor alpha (TNF-α) and cyclooxygenase II (COX-2). The activation of the NALP3 inflammasome also requires generation of ROS, which are produced following the stimulation of a respiratory burst in phagocytic cells. c-Silica can produce ROS either directly via chemical interactions on freshly cleaved surfaces (see above) or indirectly via ROS generation in macrophages (oxidative burst).

Following macrophage activation, the innate immune system responds, causing the observed inflammatory responses in the lung. However, the innate immune mechanisms underlying the observed inflammatory responses are complex and not fully understood (reviewed by Fujimura 2000; Huaux 2007; Leung et al. 2012; Weissman et al. 1996). T-lymphocyte responses have been implicated, as there is a predominance of CD4+ T cells (helper/inducer T cells) in both humans diagnosed with silicosis and animal models of silicosis. However, several animal studies have shown that T-lymphocyte responses are not essential for the development of silicosis. Furthermore, the underlying response may not be due to

inflammation exclusively, as several studies in mice show a persistent anti-inflammation response subsequent to an acute inflammation response. The anti-inflammatory response is coupled with a pro-fibrogenic response. Interleukin-10 (IL-10) is proposed to play a key role in this process. IL-10 has been shown to increase profibrotic activity via induction of TNF-α expression in conjunction with suppression of the expression of the anti-fibrotic eicosanoid PGE_2. These events are consistent with the overview shown in Figure 2-6, which proposes that persistent cycling between inflammation and repair processes (including anti-inflammatory processes) leads to pathological fibrogenesis.

Chronic Obstructive Pulmonary Disease (COPD). COPD, characterized by airflow limitation due to chronic bronchitis or emphysema, is associated with exposure to c-silica dust even in the absence of silicosis. Possible mechanisms involved in the development of c-silica-induced COPD include: (1) cellular damage, generation of ROS, and subsequent release of proinflammatory and fibrogenic factors, and (2) injury to epithelial cells, allowing c-silica to penetrate small airway walls and induce localized fibrosis (Hnizdo and Vallyathan 2003).

Lung Cancer. It is generally thought that lung cancer following c-silica exposure results from inflammation-based mechanisms secondary to silicosis; however, a direct genotoxic effect of c-silica particles cannot be ruled out (reviewed by Borm et al. 2011; Brown 2009; Checkoway and Franzblau 2000; Chen and Shi 2002; Cox 2011; Ding et al. 2002; Huaux 2007; IARC 2012; Leung et al. 2012; Mossman and Glenn 2013; Schins 2002a; Shi et al. 2001) (see Figure 2-6).

As discussed above, silicosis is associated with chronic inflammation, which triggers activation of tissue repair, proliferation, and hyperplasia of mesenchymal cells and alveolar epithelial cells. As indicated above, oncogenic transcription factors are also activated during the inflammatory process (e.g., NF_kB, AP-1). As in silicosis, it is proposed that TNF-α has a critical role in c-silica-induced lung cancer. While NF_kB leads to TNF-α release, TNF-α in turn is capable of activating NF_kB, which leads to increased survival of transformed epithelial cells. The increased survival, and subsequent division, could lead to increased pools of preneoplastic cells and ultimately neoplastic transformation. One proposed mechanism for this progression, based on studies in rat models, is epigenetic silencing of the tumor suppressor gene p16 through hypermethylation of the promotor region due to proliferative stress. Additionally, chronic inflammation results in the formation of ROS and RNS. These reactive species are thought to play a major role in DNA and cell damage, resulting in secondary, inflammation-driven genotoxicity that can lead to neoplastic changes. These inflammation-based mechanisms are proposed to have a threshold effect, as chronic inflammation occurs only following c-silica overload in the lung. This inflammation-

based mechanism of carcinogenicity is supported by epidemiological data indicating that the association between c-silica and lung cancer is stronger in individuals with silicosis than in individuals without silicosis. However, these findings could merely reflect that c-silica levels high enough to cause silicosis (and inflammation) are also capable of causing cancer, rather than indicating that silicosis is a necessary precursor for cancer development.

As discussed in Section 2.20 Genotoxicity, c-silica is a mutagenic and genotoxic agent both *in vitro* and *in vivo*. Phagocytized c-silica particles could cause DNA damage and cell transformation by directly interacting with DNA, disrupting chromosome segregation during mitosis, generation of ROS on reactive particle surfaces or during oxidative burst by macrophages, and/or depleting antioxidant defenses. This mechanism is proposed to be non-threshold in nature, and therefore does not require c-silica overload in the lung. As discussed above for silicosis, surface properties and particle size, shape, and crystallinity are also important mediators for the genotoxic potential of c-silica. For example, surface modification of quartz (to block reactive surfaces) prevents ROS generation and oxidative DNA damage *in vitro*. This mechanism of carcinogenicity is supported by epidemiological data indicating that lung cancer can occur in individuals who were not diagnosed with silicosis.

Autoimmune Disease. Information in this section is from the following reviews: Franklin et al. 2016; Huaux (2007); Lee et al. (2012, 2017); Maeda et al. (2010); Otsuki et al. (2007); Parks et al. (1999); Rimal et al. (2005); Rocha-Parise et al. (2014); Steenland and Goldsmith (1995); and Stratta et al. (2001a). c-Silica is a known immune adjuvant that can nonspecifically enhance immune responses via increased antibody production. The inflammatory response induced by c-silica is thought to underlie its adjuvant effect, potentially through IL-1 activation of T-helper cells, which facilitate B-cell production of antibodies. Therefore, c-silica exposure alone may not cause autoimmune dysfunction; rather, c-silica exposure may act as an adjuvant to promote or accelerate autoimmune disease development triggered by another factor (e.g., genetic susceptibility, pathogen or chemical exposure). Thus, the severe inflammatory response following exposure to c-silica is proposed as a common initiating step that could lead to a variety of autoimmune disorders.

Autoimmune disorders following c-silica exposure may occur secondary to silicosis, as chronic immune stimulation in the lungs is capable of causing systemic effects. For example, pulmonary inflammation can lead to release of elastase into systemic circulation, leading to thrombotic events that mildly damage vasculature. Chronic mild damage to vasculature may, in turn, lead to chronic inflammation in blood vessels, triggering vasculitis. Alternatively, autoimmune disorders may occur independently of lung

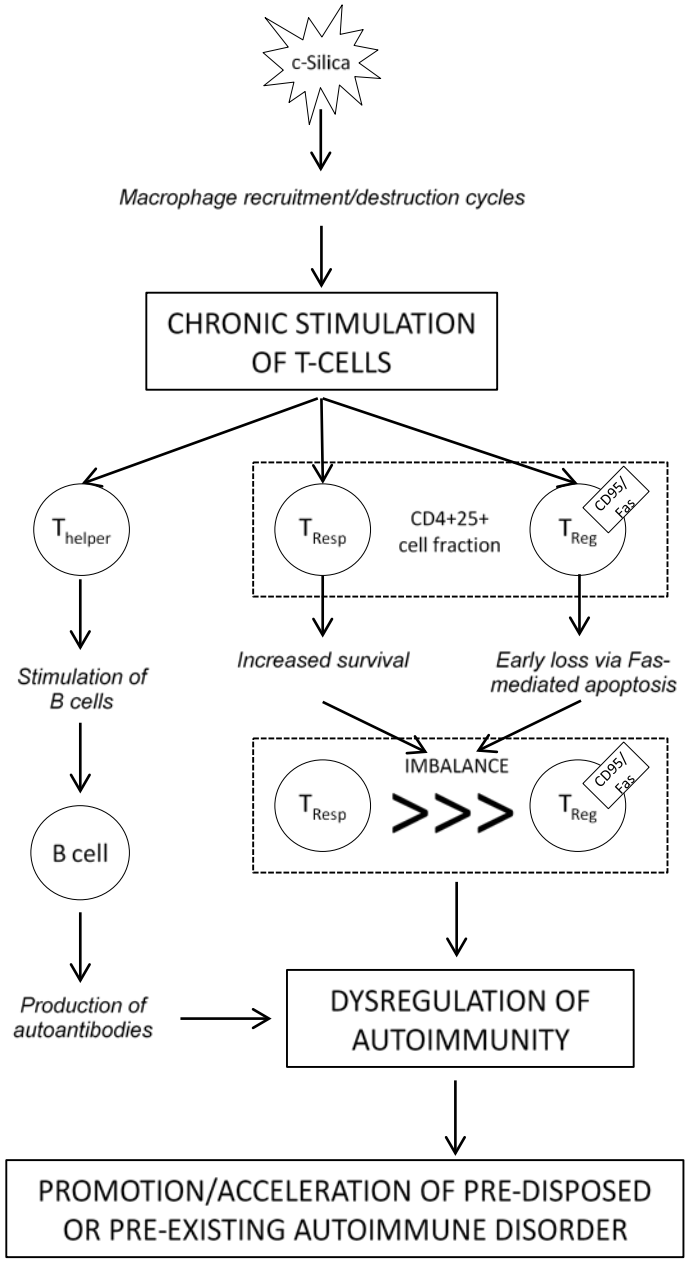
disease due to deposition of c-silica particles in the lymphatic system (transported via macrophages). In this case, macrophage destruction and recruitment cycles would occur in the lymph system (as described above in the lung), leading to stimulation of T-helper cells and B-cell production. Increased B-cell activation would explain elevated levels of autoantibodies observed in c-silica-exposed individuals, including:

- Rheumatoid factor, which is associated with rheumatoid arthritis (note that a positive rheumatoid factor also can occur with conditions other than rheumatoid arthritis);
- Anti-nuclear antigen, which is associated with systemic sclerosis (note that a positive anti-nuclear antigen may also occur other conditions and in healthy individuals);
- Anti-topoisomerase I (anti-Scl-70), which is associated with systemic sclerosis (note that a positive anti-Scl-70 also can occur with conditions other than rheumatoid arthritis);
- ANCA, which is associated with ANCA-associated vasculitis (note that a positive ANCA supports a diagnosis of systemic autoimmune vasculitis and can help distinguish between types of vasculitis);
- Anti-CD95/Fas autoantibody, which leads to increased survival of responder T-lymphocytes (autoimmune lymphoproliferative syndrome) and increased immune reactivity with self/non-self antigens; and
- Anti-caspase 8 autoantibody, which is associated with decreased Fas-mediated apoptosis in T-lymphocytes.

Recent studies have shown that c-silica specifically alters the peripheral CD4+25+ T-cell fraction, particularly the balance between T-responder and T-regulator cells mediated via Fas-dependent apoptosis (see Figure 2-7). This imbalance, in addition to excess autoantibodies produced by activated B-cells, would lead to a dysregulation of autoimmunity. The disruption would likely be subclinical; however, promotion of a pre-existing autoimmune disorder or triggering of an autoimmune disorder in a pre-disposed individual could occur.

Renal Disease. Evidence for elevated risk of renal disease has been observed in c-silica-exposed individuals, both in the presence and absence of silicosis (see Renal Effects in Section 2.10). Renal damage in c-silica-exposed individuals has been associated with two distinct mechanistic pathways: (1) direct toxic effect of excessive c-silica accumulation in the kidney and (2) indirect toxic effects secondary to autoimmune disease (as reviewed by Parks et al. 1999; Stratta et al. 2001a). In the first proposed pathway, deposition of c-silica particles in the kidney leads to chronic inflammation, which

Figure 2-7. Proposed Mechanistic Pathway Leading to Autoimmune Dysregulation Following c-Silica Exposure



c-Silica exposure causes macrophage recruitment/destruction cycles in the lymphatic system, leading to chronic stimulation of T-cells. Helper T-cells stimulate production of B-cells, which leads to increased production of autoantibodies. Both T-responder and T-regulator cells are also stimulated; however, T-regulator cells are lost from the fraction due to Fas-mediated apoptosis. This causes an imbalance in the CD4+25+ cell fraction. Together with increased production of autoantibodies, this imbalance leads to dysregulation of autoimmunity, promoting and/or accelerating autoimmune disease development triggered by another factor (e.g., genetic predisposition or other chemical exposure).

Sources: Huaux (2007); Lee et al. (2012, 2014); Maeda et al. (2010); Otsuki et al. (2007); Parks et al. (1999); Rimal et al. (2005); Steenland and Goldsmith (1995); Stratta et al. (2001a)

progresses to fibrosis in a process similar to that described above for silicosis. This type of renal damage is most often described in individuals diagnosed with silicosis, and c-silica overload would directly lead to renal failure. In the second proposed pathway, renal complications of autoimmune diseases would occur via different mechanisms depending upon the specific autoimmune disease present. For example, renal damage associated with ANCA-associated vasculitis and systemic sclerosis is associated with vascular pathology in the glomerulus, resulting in glomerulonephritis. Renal pathology associated with systemic lupus erythematosus appears to be due to deposition of autoantibodies in the kidney. It has also been proposed that protein adsorbed onto the surface of c-silica deposited in the kidney may denature, potentially acquiring antigenic properties. Subsequently, excess antibody production from chronic immune stimulation in the lung and/or lymphatic system could cross-react with renal antigens.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Overview. Throughout this section, the term silica refers to all types of silica particles. Information that is specific to c-silica or a-silica is indicated as such. The following provides a general overview of the toxicokinetics of silica compounds. Additional information on the toxicokinetics of synthetic a-silica compounds, including results of unpublished studies, was reviewed by the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006).

- Absorption:
    - Respiratory tract: Absorption of silica compounds from the respiratory tract is the most studied absorption pathway.
        - No quantitative estimates of absorption of silica compounds from the respiratory tract are available. However, detection of silica in the urine of exposed workers indicates that c-silica undergoes absorption following inhalation exposure.
        - Respiratory particles of silica are cleared from the pulmonary region primarily by lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow.
        - Due to limited solubility, dissolution of c-silica, followed by absorption from the respiratory tract is not a predominant pathway for absorption. Dissolution of a-silica compounds may be a more important absorption pathway for a-silica.
        - Inhaled c-silica compounds may be retained within the lungs for years after cessation of exposure
    - Gastrointestinal tract: Limited information from animal studies indicates that absorption of silica compounds following oral exposure is negligible.
    - Dermal: No studies examining dermal absorption of silica compounds were identified, although it is anticipated that absorption through the skin would be negligible.

- Distribution: Studies in humans and animals show that inhaled c-silica is distributed to the kidneys, lymph nodes, blood, liver, and spleen. No information on distribution of silica compounds following oral or dermal exposure was identified.

- Metabolism: Absorbed silica compounds do not undergo metabolism.

- Excretion: Silica has been detected in urine of workers exposed to c-silica. Ingested silica compounds are excreted in the feces. No information on excretion of silica compounds following dermal exposure was identified.

3.1.1 Absorption

Inhalation Exposure. Inhaled silica particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption by blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, kidney). The above processes apply to all forms of deposited silica, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size) and biological reactivity (e.g., macrophage recruitment, activation, and cytotoxicity).

Particles having diameters >5 μm deposit in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract (Bailey et al. 2007; ICRP 1994). Smaller particles (≤5 μm) are deposited primarily in the pulmonary region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow. Dissolution, which contributes to absorptive clearance of some types of particles, is negligible for c-silica because of the low solubility of c-silica particles. Dissolution may play a larger role in clearance of a-silica, and may contribute to its faster pulmonary clearance compared to c-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981).

The various processes that contribute to the clearance of silica from the respiratory tract give rise to multi-phasic lung retention kinetics (Katsnelson e al. 1992; Stober et al. 1999; Vacek et al. 1991). In most studies of lung retention, at least two kinetic components are evident. The faster phase is likely due to relatively rapid mechanical clearance mechanisms (e.g., mucociliary transport) and, for more soluble forms (e.g., a-silica), absorption to blood of soluble or relatively rapidly dissolved insoluble material deposited in the lung. The slower phase is likely due to physical transformation and dissolution and/or mechanical clearance of highly insoluble particles by phagocytosis and macrophage migration.

Rates for slow-phase clearance vary with the type of silica particle inhaled, inhaled dosage, and animal species (Kreyling 1990). In humans, slow-phase clearance of highly insoluble particles occurs with half-lives of several years (Bailey et al. 2007; ICRP 1994). The slow phase of clearance of silica particles explains the accumulation of particles in the human lung that can occur with repeated exposures to airborne silica as well as its detection in lung tissue years after cessation of exposure (Borm and Tran 2002; Case et al. 1995; Dobreva et al. 1975; Dufresne et al. 1998; Loosereewanich et al. 1995).

Studies conducted in rodents found that clearance of c-silica (quartz) was >10 times slower than a-silica (Davis 1986; Kelly and Lee 1990; Reuzel et al. 1991; Schepers 1981). A contributing factor to the slower clearance of c-silica may be its greater cytotoxic potency, related to its surface structure. In rats, clearance following inhalation of an aerosol of pure cristobalite was slower than following inhalation of aerosols of quartz, and rats showed a more pronounced lung inflammatory response to cristobalite compared to quartz (Hemenway et al. 1990). Macrophages play an important role in the mechanical clearance of silica particles (Absher et al. 1992; Brody et al.1982). A more intense inflammatory response to macrophage cytotoxicity induced by c-silica results in slow particle clearance (Donaldson and Borm 1998; Fenoglio et al. 2000; Warheit et al. 2007). In general, mechanical clearance of deposited particles appears to have a limited capacity. Macrophage-mediated clearance of respirable particles is inhibited at high particle loads. This phenomenon has been referred to as *particle overload* (Mauderly et al. 1990; Morrow 1992). The inhaled dose required to achieve particle overload is not the same in all animal species and may be lower in small mammals (Snipes 1996). Rats exhibit lower particle overload thresholds than hamsters (Saffiotti et al. 1993). Above the particle overload threshold, differences in clearance between c-silica and a-silica become less pronounced (Pratt 1983). Particle overload is an important consideration in low-dose extrapolation of dose-response relationships and in extrapolation across animal species because it may result in a nonlinear relationship between the inhaled dosages and particle burden in the lung (Lippmann and Timbrell 1990; McClellan 1990). Particle overload may also render the respiratory tract more vulnerable to other airborne particulates as a result of depressed particle clearance (Morrow 1992).

Oral Exposure. Little information regarding the gastrointestinal absorption of silica was identified. In rats, six gavage doses of 50 mg c-silica did not result in detectable silica particles in gastrointestinal submucosa or region lymph nodes, suggesting little or no transfer out of the gastrointestinal tract lumen (Gonzalez Huergo and Rojo Ortega 1991).

Dermal Exposure. Studies of dermal absorption of silica have not been reported and, given the solubility of silica dusts, dermal exposure is likely to be a minor pathway of absorption of silica. Skin samples collected from patients with progressive systemic scleroderma (PSS) and who were also exposed to c-silica (quartz dusts) showed evidence of quartz crystals in chorionic fibers, blood vessel walls, corneas, epidermal keratinocytes, and collagen fiber, based on detection of birefringent particles (Mehlhorn et al. 1990). This finding could indicate dermal absorption or dermal deposition of inhaled or ingested silica. Quartz crystals were not observed in skin tissue of patients who did not have PSS and were exposed to quartz dust, including silicosis patients.

3.1.2 Distribution

Inhalation Exposure. Few studies of distribution of silica outside of the respiratory tract have been reported (Absher et al. 1992). Evidence for associations between exposure to c-silica dusts and renal disease suggests that c-silica particles may distribute to the kidney (see Section 2.10, Inhalation, Systemic Effects). Silica has been detected in kidney tissue and urine of workers who have been exposed to c-silica, suggesting that systemic distribution can occur in humans following inhalation exposure (Giles et al. 1978; Hauglustaine et al. 1980; Ibrahim et al. 2011; Saldanha et al. 1975). Inhalation exposure of rats to c-silica shows distribution primarily to mediastinal lymph nodes and thymus; silica particles were detected in negligible amounts in the blood, kidney, liver, and spleen (Absher et al. 1992). These studies suggest that lymph may provide a mechanism for systemic distribution of silica particles (Vacek et al. 1991).

Oral Exposure. Studies of the systemic distribution of silica following oral exposures have not been reported.

Dermal Exposure. Studies of the systemic distribution of silica following dermal exposures have not been reported.

3.1.3 Metabolism

Absorbed silica is not metabolized. Although c-silica particles are highly insoluble, *in vitro* studies have found that silica particles dissolved from slate dust can bind to serum albumin (Singh et al. 1984).

3.1.4 Excretion

Inhalation Exposure. Silica has been detected in urine of ceramic factory workers exposed to c-silica, suggesting that systemic distribution can occur in humans following inhalation exposure (Ibrahim et al. 2011). Urine is an excretory pathway for silica absorbed from the respiratory tract.

Oral Exposure. Ingested silica is excreted in the feces. Absorbed silica, if absorption were to occur, may be excreted in urine; however, no studies of excretion of silica following absorption from the gastrointestinal tract have been reported.

Dermal Exposure. Studies of excretion of silica following dermal exposures have not been reported.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models for c-silica or a-silica were identified.

3.1.6 Animal-to-Human Extrapolations

Numerous animal studies examining effects of inhaled c-silica have been conducted, and have been particularly useful in investigating pulmonary clearance of particles and mechanisms of toxicity (Cox 2011; EPA 1996; NIOSH 2002). However, results of animal studies may be difficult to extrapolate to humans due to species differences in macrophage overloading, which can affect pulmonary clearance and toxicity (EPA 1996). Rats appear to be more sensitive than hamsters to macrophage overload (Saffiotti et al. 1993). Furthermore, it has been proposed that overload of lung macrophages in rats may not be relevant to humans (Snipes 1996). Regarding use of animal models to investigate the carcinogenic effects

of c-silica, c-silica is carcinogenic in rats exposed by inhalation or intratracheal instillation, but not in mice or hamsters (IARC 2012). Thus, not all experimental animals appear to be appropriate for use in extrapolation to humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to silica are discussed in Section 5.7, Populations with Potentially High Exposures.

Crystalline Silica.

Children. No information regarding susceptibility of children to c-silica or a-silica has been identified. Silicosis is considered to be an occupational disease that typically occurs with prolonged (years) exposure. The same adverse effects observed in adult workers would be expected to occur in children if sufficiently exposed. However, non-occupational exposure of children to c-silica could occur in rare circumstances (Bhagia 2012; Grobbelaar and Bateman 1991a, 1991b; Norboo et al. 1991a, 1991b; Ranavanya et al. 1992; Rees and Murphy 2007). For example, a mixed-etiology pneumoconiosis (combined exposure to c-silica, heavy dust, and heavy domestic smoke) has been reported in adults engaging in domestic maize hand-grinding activities using quartz rocks in South Africa (Grobbelaar and Bateman 1991a, 1991b). Unique geographical locations and environmental conditions may also result in elevated exposure leading to silicosis. In addition, radiographic evidence consistent with silicosis has been reported in older individuals in agricultural villages in the northwest Himalayas in India (Norboo et

al. 1991a, 1991b; Ranavanya et al. 1992). This area has frequent dust storms, producing silicotingen rock dust with high c-silica content. However, non-occupational exposure to elevated levels of c-silica that produce silicosis is very rare.

Underlying diseases. Progression of silicosis can cause serious decrements in lung function that may result in death due to respiratory failure (see Section 2.4, Inhalation, Systemic Effects, Respiratory). Thus, individuals with underlying lung and health conditions, such as asthma, emphysema, tuberculosis, and infection with human immunodeficiency virus, may be more susceptible to adverse respiratory effects of inhaled c-silica. Workers with underlying renal diseases also may be more susceptible to adverse renal effects of inhaled c-silica.

Smoking. As discussed in Section 2.19 (Inhalation, Cancer), results of recent studies show that the risk of lung cancer due to c-silica is higher in smokers than in nonsmokers. Results of a retrospective study in China examining lung cancer risk in smoking and nonsmoking c-silica workers showed a consistent increase (2.75–4.38-fold) in lung cancer risk in smokers versus nonsmokers over stratified exposure quartiles (Liu et al. 2013). The study authors stated that 'the joint effect of *[c-]*silica and smoking was more than additive and close to multiplicative."

Polymorphisms. Information in this section is from the following reviews: Ding et al. 2002; Gomez-Puerta et al. 2013; Iannello et al. 2002; IARC 2012; NIOSH 2002; Parks et al. 1999; Yucesoy et al. 2002.

Specific growth factors and cytokines have been identified as playing a crucial role in the pathogenesis of silicosis, particularly TNF-α or IL-1 (see Section 2.20.2 Mechanisms of Toxicity for more details). Evidence from human studies indicates that certain polymorphisms for TNF-α or IL-1 are associated with increased incidence and/or severity of silicosis following occupational exposure to c-silica. For example, in silicotic patients, the risk of developing severe fibrosis was associated with the HLA-Aw19-B18 TNF-α haplotype in the Caucasian population and the HLA-Bw54 TNF-α haplotype in the Japanese population. In a case-control study, the TNF-α variant (-238) was significantly associated with severe silicosis and the TNF-α (-308), IL-1RA (+2018), and IL-1RA (-208) variants were significantly associated with moderate and severe silicosis.

Allelic variants of TNF-α or IL-1 have also been associated with autoimmune and inflammatory diseases. For example, individuals with the HLA-DR3 TNF-α haplotype or a minor variant of the IL-1RA VNTR in linkage disequilibrium have a genetic predisposition to SLE. Therefore, individuals with

polymorphisms in these genes may also have increased susceptibility to autoimmune effects associated with occupational exposure to c-silica. In addition, individuals with other known genetic predispositions to autoimmune disease may have an increased risk of autoimmune dysfunction with occupational exposure to c-silica (e.g., genetic alterations in the major histocompatibility complex). For example, only specific strains of mice (NZB and MRL/MpJ) develop autoimmune pathology resembling SLE following exposure to c-silica dust.

A case-control study of workers with silicosis evaluated interactions between c-silica exposure and polymorphisms for genes encoding for components of the Napl3 inflammasome (Nalp3, caspase-1, IL-1β) (Weng et al. 2015). The Napl3 inflammasome is a multiprotein oligomer that activates inflammatory responses. The study population included 179 Chinese iron miners with silicosis and 201 controls. Results indicate that polymorphisms in Nalp3 and caspase-1 may be involved in individual susceptibility in workers with silicosis, and that there are interactions between polymorphisms and cumulative exposure, age, and smoking status.

Altitude. In a recent review, Vearrier and Greenberg (2011) concluded that workers at high altitude are at risk for more rapid development and progression of silicosis.

Amorphous Silica. No specific information regarding susceptible populations for a-silica was identified. Animal studies identify the respiratory tract as the primary target for inhaled a-silica; therefore, individuals with underlying respiratory disease may be more susceptible to the adverse respiratory effects of a-silica.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to silica are discussed in Section 3.3.1. The National Report on Human Exposure to

Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for silica from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by silica are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure to Silica

Crystalline Silica and Amorphous Silica. Silica has been detected in urine of ceramic factory workers exposed to c-silica, indicating that systemic distribution occurs in humans following inhalation exposure (Ibrahim et al. 2011). Thus, the presence of silica in the urine indicates that exposure has taken place. a-Silica is excreted in the feces. The source of fecal silica is most likely from unabsorbed particles of inhaled silica that are deposited in the oral cavity and swallowed or are cleared from the airway by muco-ciliary clearance and subsequently swallowed. However, the quantitative relationship between urinary silica and cumulative exposure is unknown. Thus, no biomarkers of exposure to c- or a-silica have been identified.

3.3.2 Biomarkers of Effect Caused by Silica

No biomarkers have been identified to characterize effects caused by c-silica or a-silica. 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). Although associations have been observed, the biomarkers examined are not specific for exposure to silica or as markers of silicosis or pre-silicosis. Elevation of these markers also may be caused by exposure to many other chemicals and by diseases involving inflammatory processes or oxidative stress. Therefore, at this time, no reliable biomarkers for silica effects or for early detection of silica exposure-induced toxicity have been established.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Crystalline Silica. As discussed in Section 2.19 (Inhalation, Cancer), results of recent studies show that the risk of lung cancer due to c-silica is higher in smokers than in nonsmokers. Results of a retrospective study in China examining lung cancer risk in smoking and nonsmoking c-silica-exposed workers showed a consistent increase (2.75–4.38-fold) in lung cancer risk in smokers versus nonsmokers over stratified exposure quartiles (Liu et al. 2013). The study authors stated that ‘the joint effect of [c-]silica and smoking was more than additive and close to multiplicative.” In addition, different c-silica industries may involve co-exposures with other chemicals (e.g., radon, metals, trace elements, asbestos, formaldehyde, benz[a]pyrene) that could potentially increase the toxicity of inhaled c-silica.

Amorphous silica. No studies on interactions of a-silica with other chemicals were identified.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The synonyms, trade names, chemical formulas, and identification numbers of silica and selected forms of silica are provided in Table 4-1.

Table 4-1. Chemical Identity of Silica and Compounds[a]

Characteristic	Information		
Chemical form	Various crystalline and amorphous silica forms		
Chemical name	Silica		
Synonym(s)	Silicon dioxide; diatomaceous earth; diatomaceous silica; diatomite, precipitated amorphous silica; silica gel, silicon dioxide (amorphous); silica colloidal[b,c]		
Registered trade name(s)	No data		
Chemical formula	SiO_2		
Chemical structure	Not applicable		
CAS Registry Number	7631-86-9		
Chemical form	Crystalline silica		
Chemical name	Quartz	Cristobalite	Tridymite
Synonym(s)	α-Quartz; quartz; agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Silica, crystalline-cristobalite; α-cristobalite; β-cristobalite	Silica, crystalline-tridymite; α-tridymite; β1-tridymite; β2-tridymite
Registered trade name(s)	CSQZ; DQ 12; Min-U-Sil; Sil-Co-Sil; Snowit; Sykron F300; Sykron F600	No data	No data
Chemical formula	SiO_2	SiO_2	SiO_2
Chemical structure	α-Quartz: trigonal crystal	α-Cristobalite: tetragonal crystal	α-Tridymite: orthorhombic crystal
CAS Registry Number	14808-60-7	14464-46-1	15468-32-3

Table 4-1. Chemical Identity of Silica and Compounds[a]

Characteristic	Information			
Chemical form	Natural amorphous silica[d]			
Chemical name	Diatomaceous earth, uncalcined	Diatomaceous earth, flux-calcined	Diatomaceous earth, calcined	Vitreous silica[e]
Synonym(s)	Kieselguhr; Diatomite; Siliceous earth; diatomaceous earth, natural	Kieselguhr, soda ash flux-calcined; Diatomite	Kieselguhr, calcined; Calcined diatomite	Fused silica, quartz glass, volcanic glass, silica glass
Registered trade name(s)	Extrelut; Celatom; Celite; Chromaton; Chromosorb; Clarcel; Decalite; Fina/Optima; Skamol	Celite; Clarcel; Decalite; Chromosorb	Celite; Claracel; Decalite	Accusand, Admafine, Borsil P, Denka F, Fusiflex, Optosil, Rancosil, Siltex, Spectrosil, Suprasil, TAFQ, Vitreosil IR,
Crystalline content (%)	2	2.2 – 10.3	58.1 – 62.7	No data
Chemical formula	SiO_2	SiO_2	SiO_2	SiO_2
Chemical structure	Not applicable[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]
CAS Registry Number	61790-53-2	68855-54-9	91053-39-3	60676-86-0
Chemical form	Amorphous silica byproduct[d]			
Chemical name	Silica fume[g]			
Synonym(s)	Amorphous silica fume			
Crystalline content (%)	6–8[h]			
Registered trade name(s)	Not applicable			
Chemical formula	SiO_2			
Chemical structure	Not applicable[f]			
CAS Registry Number	69012-64-2			

Table 4-1. Chemical Identity of Silica and Compounds[a]

Characteristic	Information			
Chemical form	Synthetic amorphous silica			
Chemical name	Pyrogenic silica	Precipitated silica	Silica gel	Colloidal silica
Synonym(s)	Fumed silica	Silica, amorphous-precipitated silica		Silica sol[i]
Registered trade name(s)	Aerosil, Cab-O-Sil, HKD, Reolosil	FK; Hi-Sil; Ketjensil; Neosyl; Nipsil; Sident; Sipernat; Spherosil; Tixosil; Ultrasil; Zeosil[j]; Zeofree[k]	Art Sorb; Britesorb; Diamantgel; Gasil; KC-Trockenperlen; Lucilite; Silcron; Silica-Perlen; Silica-Pulver; Sylobloc; Syloid; Sylopute; Trisyl	Baykisol, Bindzil, Hispacil, Ludox, Nalcoag, Nyacol, Seahostar, Snowtex, Syton
Chemical formula	SiO_2	SiO_2	SiO_2	SiO_2
Chemical structure	Not applicable[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]
CAS Registry Number	112945-52-5	112926-00-8	63231-67-4	NA[l]

[a]All information obtained from IARC (1997) and ChemID (2019) except where noted.
[b]Associated chemical (HSDB 2009, 2012).
[c]NIOSH 2015a, 2015b.
[d]Natural a-Silica and silica fume may contain c-silica; c-silica content varies based on methods of preparation and purification (IARC 1997).
[e]Vitreous silica can be formed naturally (volcanic glass, fusion of siliceous earth following meteorite or lightening impact), unintentionally as a by-product during certain industrial processes, or intentionally as a synthetic a-silica by heating c-silica and then cooling it rapidly to avoid recrystallization. Both natural and synthetic forms may contain small amounts of c-silica. (Fruijtier-Polloth 2012; Arts et al. 2007; Smith 2006; IARC 1997)
[f]Amorphous, randomly linked silicon and oxygen tetrahedral units with no defined pattern.
[g]By-product formed unintentionally during certain industrial processes (e.g., manufacture of ferrosilicon and silicon). (Fruijtier-Polloth 2012; Arts et al. 2007; IARC 1997). Silica fume produced as a by-product can then be used in certain manufacturing processes (Florke et al. 2008).
[h]Swensson et al. 1971.
[i]Florke et al. 2008.
[j]Arts et al. 2007.
[k]Warheit et al. 1995.
[l]Colloidal silica does not have a unique CAS Registry Number; it is included in the general silicon dioxide CAS Registry Number (7631-86-9).

CAS = Chemical Abstracts Service; NA = not applicable

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of selected c-silica, natural a-silica, and synthetic a-silica compounds is provided in Tables 4-2, 4-3, and 4-4, respectively.

Table 4-2. Physical and Chemical Properties of Crystalline Silica Compounds[a]

Property	Information		
Chemical name	Quartz	Cristobalite	Tridymite
Molecular weight	60.1	60.1	60.1
Color	Colorless, white, black, purple, or green solid	Colorless, white, or yellowish solid	Colorless or white solid
Physical state	Solid	Solid	Solid
Melting point (°C)[b]	573 (α-quartz converts to β-quartz); 870 (β-quartz converts to tridymite)	1,713	1,470 (tridymite converts to cristobalite)
Boiling point (°C)	2,230	2,230	2,230
Density (g/cm^3) at 20°C[c]	2.648 (α-quartz)	2.334	2.265
Odor	Odorless	Odorless	Odorless
Odor threshold:			
Water	Not applicable	Not applicable	Not applicable
Air	Not applicable	Not applicable	Not applicable
Solubility:			
Water at 20°C	Insoluble	Insoluble	Insoluble
Other solvents	Dissolves in hydrofluoric acid but insoluble in most other acids and organic solvents[d]	Dissolves in hydrofluoric acid	Dissolves in hydrofluoric acid
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	No data	No data
Henry's law constant at 25°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m^3)	No data	No data	No data
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB (2009, 2012) except where noted.
[b]IARC 1997.
[c]Haynes et al. 2014.
[d]EPA 1996.

Table 4-3. Physical and Chemical Properties of Natural Amorphous Silica Compounds[a,b]

Property	Information			
Chemical name	Diatomaceous earth, uncalcined	Diatomaceous earth, flux-calcined	Diatomaceous earth, calcined	Vitreous silica[c]
Molecular weight	60.1	60.1	60.1	60.1
Color	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder
Physical state	Solid	Solid	Solid	Solid
Melting point (°C)	1,710	1,710	1,710	1,713[d]
Boiling point (°C)	2,230	2,230	2,230	2,230
Density (g/cm^3) at 20°C	2.2 at 25°C	2.2 at 25°C	2.2 at 25°C	2.196[d]
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20°C	Poorly to insoluble	Poorly to insoluble	Poorly to insoluble	Poorly to insoluble
Other solvents	No data	No data	No data	Dissolves in hydrofluoric acid
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C
Henry's law constant at 25°C	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors (ppm to mg/m^3)	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

[a]All information obtained from HSDB (2009, 2012) except where noted.
[b]Natural forms of a-Silica may contain c-silica; c-silica content varies based on methods of preparation and purification (IARC 1997).
[c]Vitreous silica can be formed naturally (volcanic glass, fusion of siliceous earth following meteorite or lightening impact), unintentionally as a by-product during certain industrial processes, or intentionally as a synthetic a-silica by heating c-silica and then cooling it rapidly to avoid recrystallization.(Fruijtier-Polloth 2012; Arts et al. 2007; Smith 2006; IARC 1997)
[d]IARC 1997.

Table 4-4. Physical and Chemical Properties of Synthetic Amorphous Silica Compounds[a]

Property	Information			
Chemical name	Precipitated silica	Pyrogenic silica	Silica gel	Colloidal
Molecular weight	60.1	60.1	60.1	60.1
Color	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder	Colorless crystals or white powder
Physical state	Solid	Solid	Solid	Dispersion in aqueous solution[b]
Melting point (°C)	1,710	1,710	1,710	1,710
Boiling point (°C)	2,230	2,230	2,230	2,230
Density (g/cm^3) at 25°C	2.2 at 25°C	2.2 at 25°C	2.2 at 25°C	2.2 at 25°C
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility[c]:				
Water at 20°C	Poorly to insoluble 80–130 ppm[d]	Poorly to insoluble	Poorly to insoluble	Colloidal dispersions with water[e]
Other solvents	No data	No data	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure (mmHg) at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C	Negligible at 20°C
Henry's law constant at 25°C	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors (ppm to mg/m^3)	No data	No data	No data	No data

[a]All information obtained from HSDB (2009, 2012) except where noted.
[b]IARC 1997.
[c]The solubility of silica is influenced by several factors including temperature and pH; it is affected by the presence of trace metals and the rate of solubility is dependent on the particle size and presence of an external a-silica layer on the particle surface (IARC 1997).
[d]EPA 1996.
[e]Fruijtier-Polloth 2012.

Silica occurs naturally in crystalline and amorphous (or non-crystalline) forms, herein referred to as c-silica and a-silica, respectively. Silica has one general Chemical Abstract Service registry number (CASRN 7631-86-9) and more specific CASRNs for individual silica forms and preparations. Both the crystalline and amorphous forms of silica are composed of a 1:2 net ratio of silicon atoms to oxygen atoms, corresponding to an empirical formula of SiO_2 and the chemical name silicon dioxide (IARC 1997). All silica compounds are silicon dioxide. The internal chemical structure of most forms of silica consists of each silicon atom bonded to four oxygen atoms in a silicon and oxygen tetrahedral (SiO_4) or pyramidal unit with four triangular sides. Crystalline forms of silica have regular, repeating three-dimensional patterns with internal oxygen atoms shared between two tetrahedral silicon atoms. Terminal oxygen atoms are negatively charged ions at environmentally relevant pH (OSHA 2013c). Amorphous forms of silica are composed of highly disordered, randomly linked silicon and oxygen tetrahedral units with no defined pattern. X-ray diffraction patterns distinguish crystalline polymorphs from each other and c-silica from a-silica.

The surface properties of silica compounds, even the same polymorph, vary. 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. In contrast, heating silica results in condensation of pairs of silanols to form siloxane bridges. In general, c-silica surfaces tend to have more order, although some c-silica is found with an outer layer of a-silica. Naturally occurring a-silica may contain a c-silica component from exposure to high temperatures and pressures (e.g., flux calcination). Grinding silica results in either heterolytic cleavage or homolytic cleavage of silicon-oxygen bonds at the surface interfaces producing Si^+ and SiO^- surface charges or surface radicals, respectively (Fubini et al. 1995). The total concentration and arrangement of silanol on the surface of c- and a-silica can vary greatly. 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. As discussed in Sections 1.2 and 2.20.2, the biological activity of both c-silica and a-silica polymorphs is affected by surface chemistry of the silica particle (Donaldson and Borm 1998; Greenberg et al. 2007; Guthrie 1995; Mossman and Churg 1998; Mossman and Glenn 2013).

c-Silica is polymorphic, meaning that there are several distinctly different crystalline forms with the same chemical composition. c-Silica polymorphs have regular, repeating three-dimensional patterns with long-range order; however, discernable variations in tetrahedral orientation and crystal symmetry differentiate the polymorphs. c-Silica is often referred to as quartz. Quartz is the most common naturally occurring

form of silica and is the second most common mineral in the world (USGS 1992). Other common forms of c-silica are tridymite and cristobalite, and less common forms of c-silica are keatite, coesite, stishovite, amethyst, and moganite (NIOSH 2002). Interconversion of the silica polymorphs occurs upon heating or cooling (see Section 5.4.2 for additional information).

The term 'free silica' refers to pure c-silica. Major impurities in c-silica polymorphs include aluminum, iron, titanium, lithium, sodium, potassium, and calcium ions (IARC 1997). The concentration of these impurities varies depending on the sample source, but is generally <1.0% in weight as oxide. Natural quartz may contain elemental impurities that are substitutions for silicon. Elemental impurities may also be present as internal or surface defects (Guthrie 1995). c-Silica substances containing other elements, such as sodium, potassium, calcium, magnesium, iron, and aluminum substituted into the crystalline matrix, are referred to as silicates (EPA 1996; USGS 1992).

a-Silica is composed of a random network of tetrahedral silica, and does not display long-range order. a-Silica forms are classified as natural or synthetic a-silica based on their origin. Natural a-silica, such as raw diatomaceous earth, contains small amounts of c-silica (mostly quartz); however, calcined and flux calcined diatomaceous earth can have cristobalite concentrations up to approximately 10 and 60%, respectively (IARC 1997). Sometimes, a-silica (silica fume, vitreous silica) is unintentionally formed during certain industrial processes, such as manufacture of ferrosilicon and silicons; these forms of a-silica are also often contaminated with c-silica (Arts et al. 2007; Fruijtier-Polloth 2012; IARC 1997). Vitreous silica can also be intentionally produced synthetically by melting c-silica and rapidly cooling to prevent recrystallization (Smith 2006). In general, other forms of synthetic a-silica are free of c-silica. They are further classified by their preparation method; there are wet process silica forms, which include precipitated silica, silica gels, and colloidal silica, and thermal process silica forms, including pyrogenic (or fumed) silica (Fruijtier-Polloth 2012; IARC 1997). Surface-modified silica is physically or chemically treated a-silica (IARC 1997).

Silica is a stable oxide of silicon. c-Silica does not readily react with most acids, but does react with hydrofluoric acid to produce silicon tetrafluoride gas (IARC 2012; OSHA 2013c). c-Silica also reacts with alkaline aqueous solutions and catechol (IARC 2012). a-Silica will react with mineral acids and alkaline solutions (OSHA 2013c).

In general, silica is considered poorly water soluble and chemically unreactive in the environment (EPA 1991; IARC 1997). The water solubility of silica has some variation due to differences in trace metal

impurities and hydration (OSHA 2013c). Solubility is lower for c-silica polymorphs than for a-silica, and anhydrous a-silica dissolves less rapidly than hydrated a-silica (IARC 1997). a-Silica dissolves in water to form monosilicic acid (Waddell 2006). External conditions such as higher temperatures and pH increase the water solubility of silica. The hydrophilicity of c-silica particles increases in humid conditions because an external layer of hydroxylated silica (silanol; SiOH) forms on the surface of the particles. Fresh surfaces of silica exposed by fracture are highly reactive and have a propensity to produce surface radicals; however, the surface is inactivated once hydrated (Costa et al. 1991; Fubini et al. 1995). Aged quartz has an external amorphous layer, referred to as a Beilby layer. The Beilby layer is more water soluble than the underlying c-silica (IARC 1997; OSHA 2013c).

Particle size has also been found to influence the rate of solubility. Silica particulate surface areas and sizes are distinguishable based on their source. Ground vitreous silica and c-silica particles have acute edges and heterogeneous particle sizes; surface areas range from 0.1 and 10 to 15 m^2/g (IARC 1997). Diatomaceous earth and cristobalite particles from diatomaceous earth are found in a variety of shapes and surface areas. Calcinated diatomaceous earth particles have surface areas that range from 2 to 20 m^2/g. Pyrogenic a-silica particles are nonporous, smooth, round aggregates with surface areas that range from 50 to 400 m^2/g. Precipitated a-silica particles have sizes and porous structures that vary in surface area from 50 to approximately 1,000 m^2/g, depending on the procedure used in their preparation. Nanoscale forms of silica with a mean particle size in the nanoparticle range (≤100 nm) are not included in this profile. However, while synthetic a-silica compounds have initial particle sizes in the nanoparticle range, these particles covalently bond during the manufacturing process to form indivisible aggregates in the respirable range, which can further combine to form micron-sized agglomerates (Fruijtier-Polloth 2012, 2016; IARC 1997; Merget et al. 2002; Taeger et al. 2016; Waddell et al. 2006); see Table 4-5. Of the synthetic a-silica compounds, only colloidal dispersions have been shown to contain stable isolated nanoparticles in addition to aggregates in the respirable range (Fruijtier-Polloth 2012, 2016).

Table 4-5. Particle Size Data for Synthetic Amorphous Silica Compounds[a]

Property	Information			
Chemical name	Precipitated silica	Pyrogenic silica	Silica gel	Colloidal
Average primary particle size (nM)	5–100	5–50	1–100	4–60
Aggregate size (µM)	0.1–40	0.1–1	0.1–25	0.1–1
Agglomerate size (µM)	1–250	1–250	NA	1–250

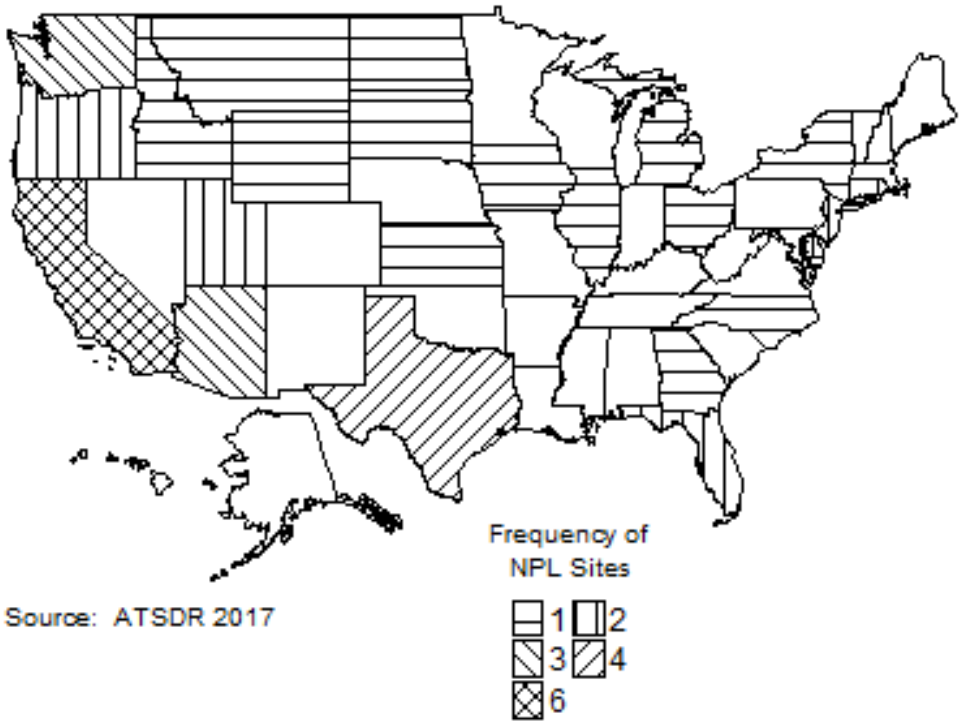
[a]Particle size ranges combined from several sources to be inclusive of reported data (Fruijtier-Polloth 2012; IARC 1997; Merget et al. 2002; Waddell et al. 2006).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Silica has been identified in at least 37 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which silica has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Silica Contamination



Crystalline Silica

- c-Silica is ubiquitous and widespread in the environment, primarily in the form of quartz. Other predominant forms include cristobalite and tridymite.
- Sand, gravel, and quartz crystal are the predominant commercial product categories for c-silica.
- c-Silica enters environmental media naturally through the weathering of rocks and minerals and anthropogenic releases of c-silica in the form of air emissions (e.g., industrial quarrying and mining, metallurgic manufacturing, power plant emissions) or use in water filtration (quartz sand).

- c-Silica undergoes atmospheric transport as a fractional component of particulate emissions, is virtually insoluble in water and generally settles into sediment, and remains unchanged in soil.
- c-Silica is present in air and water; therefore, the general population will be exposed to c-silica by inhalation of ambient air and ingestion of water.
- Inhalation exposure is the most important route of exposure to c-silica compounds due to the development of adverse effects from inhaled c-silica in occupational settings.
- Individuals with potentially high exposures include workers with occupational exposure to c-silica, which occurs during the mining and processing of metals, nonmetals, and coal, and in many other industries.

Amorphous Silica

- 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). Vitreous silica can also be intentionally produced, or may occur with a-silica fume as a by-product during certain industrial processes.
- a-Silica is used in a wide variety of industrial processes and consumer products (e.g., filtration systems, desiccants/absorbants, fillers, thickeners, pesticides, food additives, food wrappings, pharmaceuticals, cleaning products, cosmetic and personal hygiene products).
- Natural a-silica enters environmental media naturally primarily through biogenic sources (e.g., diatoms).
- Both natural and synthetic a-silica enter environmental media through anthropogenic releases of silica in the form of air emissions (e.g., industrial quarrying and mining, metallurgic manufacturing, power plant emissions), use in water filtration (diatomaceous earth), industrial waste waters (synthetic a-silica), or use as a pesticide (diatomaceous earth, a-silica gel).
- a-Silica undergoes atmospheric transport as a fractional component of particulate emissions, is poorly soluble in water (although does dissolve to some degree) and mainly settles into sediment, and remains unchanged in soil. Aquatic and terrestrial plants uptake bioavailable forms of a-silica from sediment and soil, respectively.
- a-Silica is present in air and water; therefore, the general population will be exposed to a-silica by inhalation of ambient air and ingestion of water.
- Synthetic a-silica also is used as an additive in food and in food packaging; therefore, food is expected to be a source of exposure to a-silica for most people.

- Inhalation exposure is expected to be the most important route of exposure to a-silica compounds due to the development of adverse effects in animals from inhaled a-silica.
- Individuals with potentially high exposures include individuals with occupational exposure to a-silica, which may occur during the mining and processing of diatomaceous earth, metallurgic manufacturing, use or manufacture of synthetic a-silicas, and sugarcane and rice farming.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

No information is available in the TRI database on facilities that manufacture or process silica because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005).

Crystalline Silica. c-Silica exists in the natural environment (OSHA 2013c). Sand, gravel, and quartz crystals are the predominant commercial product categories for c-silica (IARC 2012). c-Silica is a common component of igneous rocks such as granite, rhyolite, quartz diorite, quartz monzonite, and andesite. Naturally occurring c-silica is mined from the earth's crust (USGS 1992). Typically, c-silica is mined using open pit or dredging methods with standard mining equipment (USGS 2014b). The major component of sand and gravel is quartz. The quartz content of crushed stone varies from region to region.

The U.S. Geological Survey (USGS 2015) reported sand and gravel in two mineral commodity summaries, industrial sand and gravel or commercial sand and gravel. An estimated 139 million metric tons of silica, in the form of industrial sand and gravel, were produced throughout the world in 2012 (USGS 2014b). The United States (50.7 million metric tons), Italy (16.4 million metric tons), Germany (7.5 million metric tons), Turkey (7 million metric tons), France (6.3 million metric tons), Australia (5.3 million metric tons), Spain (5 million metric tons), the United Kingdom (3.8 million metric tons), and Japan (3.2 million metric tons) were the highest producing countries in 2012. The USGS performed a voluntary survey in 2012 of U.S. industrial sand and gravel producers from 77 operations, which represented 75% of the U.S. total production (combined). The survey data indicated that the Midwest produced over half (56%) of the 50.7 metric tons of industrial sand and gravel produced in the United States, followed by the South at 36%, the West at 5%, and the Northeast at 3% (USGS 2014b). Demand

for hydraulic fracturing sand has resulted in increased industrial sand and gravel production capacity in the United States through ongoing permitting and opening of new mines (USGS 2015).

In 2012, the United States produced 812 million metric tons of construction sand and gravel (USGS 2014c). Construction sand and gravel were produced by 4,100 companies and government agencies in the United States (USGS 2015). Texas, California, Minnesota, Washington, Michigan, Colorado, Arizona, North Dakota, Wisconsin, and Ohio accounted for about 55% of total U.S. output.

Quartz crystal for electronics is predominantly from cultured, not natural, crystal. Synthetic quartz crystals are grown in specific shapes and sizes in heavy-duty autoclaves at 1,500–20,000 pounds/inch^2 and 250–450°C (USGS 1992). No companies in the United States reported production of cultured quartz crystal in a 2012 USGS voluntary survey (USGS 2014b). Cultured quartz crystal is produced primarily in Asia.

Quartz has two forms, α-quartz and β-quartz. The thermodynamically stable form of quartz under ambient conditions is α-quartz; β-quartz forms at temperatures >573°C (USGS 1992). Quartz has a range of physical forms with different sizes, shapes, surface area, roughness, and sorption capacity. Natural quartz is collected from ore through a beneficiation process where raw material is milled and ground into particles and separated into desired mineral and waste. Grinding of sand or gravel is sometimes required to achieve a desired silica material; these processes increase the levels of dust containing respirable c-silica (NTP 2014). Idiomorphic quartz, lump quartz, quartz pebbles, granular quartz, quartz sand, quartz powder, and quartz rock are quartz raw material forms (Florke et al. 2008). Silica flour is an extremely fine-grade silica sand product. Tripoli (CASRN 1317-95-9) is a form of microcrystalline quartz with an extremely small particle size (NIOSH 2011).

Cristobalite is a form of c-silica formed at temperatures >1,470°C (OSHA 2013c). Cristobalite may be formed from quartz during the pouring of metal in foundries where quartz is used to make molds and cores (IARC 1997). Tridymite is a form of c-silica formed at temperatures >870°C (OSHA 2013c). Both cristobalite and tridymite are found in volcanic rocks and glass (Mossman and Glenn 2013).

Flint, chalcedony, agate, chert, and novaculit are cryptocrystalline silica. Cryptocrystalline silica is silica with submicrometer crystals formed by geological crystallization or compaction of a-silica (IARC 1997; USGS 1992). Forms of c-silica are gemstones (USGS 2014a, 2015). The estimated values in 2012 of U.S. natural quartz gemstone production were $383,000 and $261,000 for macrocrystalline and

cryptocrystalline quartz, respectively (quantity in mass not reported). The macrocrystalline quartz gemstones are amethyst, aventurine, blue quartz, citrine, hawk's eye, pasiolite, prase, quartz cat's eye, rock crystal, rose quartz, smoky quartz, and tiger's eye; the cryptocrystalline quartz gemstones are agate, carnelian, chalcedony, chrysoprase, fossilized wood, heliotrope, jasper, moss agate, onyx, and sard.

Amorphous Silica. Biogenic silica is naturally occurring a-silica from living matter, such as plants and diatoms, radiolarians, or silicoflagellates. Certain species of plants and animals, known as diatoms and radiolarians, respectively, extract dissolved a-silica from their aqueous environment to form structures and shells (USGS 1992). Diatoms and radiolarians are biological sources of a-silica. The remains of diatoms and radiolarians in sediment can harden into diatomite and radiolarite. Diatomite, which is also known as Kieselguhr or diatomaceous earth, is a loosely coherent, chalk-like sediment that contains up to 94% SiO_2 (0.1–4.0% c-silica) (IARC 1987). Aluminum oxide, iron (III) oxide, titanium dioxide, and calcium, magnesium, sodium, and potassium ions are common impurities in diatomite (IARC 1997). High-temperature calcined and high-temperature flux-calcined diatomaceous earth may contain cristobalite, formed during the calcination process of diatomaceous earth (Mossman and Glenn 2013). Flux-calcined diatomaceous earth is produced when diatomite is heated with flux and typically contains between 40 and 60% cristobalite (OSHA 2013c).

Raw diatomaceous earth is obtained through open pit mining (Checkoway et al. 1993). In 2014, an estimated 800,000 tons of diatomite was produced at 11 mining areas and 9 processing facilities in California, Nevada, Oregon, and Washington (USGS 2015). In 2015, national aggregate production volumes were 50,000,000–100,000,000 pounds for raw diatomaceous earth and 500,000,000–750,000,000 pounds for flux-calcined diatomaceous earth (CDR 2017). The estimated world mine reserves of diatomite is large (>360 million metric tons). In 2014, total (world) mine production was 2.36 million metric tons, with 800,000 metric tons in the United States, 430,000 metric tons in China, and 325,000 metric tons in Denmark. The largest diatomite deposits in the world are located in Lompoc, California (Florke et al. 2008). Diatomites are also mined in Georgia, Mississippi, Nevada, Oregon, and Washington.

Vitreous silica (or fused silica), also known as volcanic or silica glass, can be formed naturally by the fusion of siliceous earth following volcanic eruptions, lightning strikes, or meteorite impact (Arts et al. 2007; Fruijtier-Polloth 2012). This glassy silica can also be formed intentionally or unintentionally during certain industrial processes when c-silica is melted and rapidly cooled, preventing recrystallization (Florke et al. 2008; Fruijtier-Polloth 2012; Merget et al. 2002; IARC 1997; Smith 2006). Vitreous silica

is also formed by vapor-phase hydrolysis of silicon tetrachloride in a methane oxygen flame. Transparent fused silica is formed from exposing 15 nm silica particles to 1,200°C and 13.8 MPa (2,000 psi) or by electric arc fusion of pure silica sand (Waddell 2006). Silica fume is also a form of a-silica that is generated unintentionally during some metallurgic processes, such as manufacture of ferrosilicon and silicon. (Fruijtier-Polloth 2012; IARC 1997). This method of silica fume generation can be used to intentionally form silica fume to be used in certain manufacturing processes (Florke et al. 2008). Silica fume is not the same as synthetic fumed (or pyrogenic) a-silica, which is discussed below. Both vitreous silica and silica fume often contain small amounts of c-silica (Arts et al. 2007; IARC 1997; Merget et al. 2002). In 2015, national aggregate production volumes of vitreous silica and silica fume were 100,000,000–250,000,000 pounds (CDR 2017).

Synthetic a-silicas are intentionally manufactured forms of a-silica with high purity and generally no detectable amounts of c-silica. There are two main processes, a thermal process (pyrogenic silica) and a wet process (silica gel, precipitated silica, colloidal silica) (Fruijtier-Polloth 2012; Merget et al. 2002). Synthetic a-silica products are often surface-treated to create hydrophobic compounds such as silica dimethicone silylate or silica silylate. The highest synthetic a-silica production capacity in 2004 was in Europe (36%), followed by North America (26%), China (25%; estimated), and Japan (13%) (Waddell 2006). National aggregate production volumes specifically reported for pyrogenic a-silica and a-silica gel were 1,000,000–10,000,000 pounds in 2015 (CDR 2017). For precipitated a-silica, national aggregate production volumes were 498,843,155 pounds in 2011 (CDR 2014); production volume data were withheld in 2012–2015 (CDR 2017). Since colloidal silica does not have a unique CASRN, specific production volume data are not available.

Pyrogenic (or fumed) silica is typically >99.8% silica (IARC 1997). It is prepared by combustion of a volatile silica at temperatures ranging from 1,200 to 2,000°C or oxidizing organic or inorganic silicon compounds (Fruijtier-Polloth 2012; IARC 1997; Waddell 2006). Precipitated silica and silica gel are finely divided synthetic a-silica produced by precipitation from a vapor or solution (EPA 1996). The precipitates are filtered, washed, and dehydrated, which reduce metal oxide impurities to 100–1,000 ppm (Fruijtier-Polloth 2012; IARC 1997). Changing parameters during these processes allows for control of physical parameters, including porosity, pore size, and surface area. Precipitated silica have a broad meso-macroporous pore structure, while silica gels are hydrous silica with an interconnected random array of spheroidal particles with a narrow microporous or mesoporous structure and average pore diameters of 2–50 nm (Florke et al. 2008; Fruijtier-Polloth 2012). Silica gel is produced when aqueous alkali metal silicate is neutralized under acidic conditions, initiating the polymerization of a-silica into

small spheroids. Silica gel has three variations referred to as hydrogel, aerogel, and xerogel based on the production method used (Waddell 2006). Colloidal silica is produced in a manner similar to silica gel; however, SiO_2 concentrations are kept low (10–15%) and the pH is maintained at a slightly alkaline level during production. This allows the subunits to stay separate and form a stable dispersion (Fruijtier-Polloth 2012). The suspension is stabilized chemically (e.g., KOH, NaOH, NH_3, HCl) or via electrostatic repulsion of particles (substitution of some silica atoms with aluminum) (Fruijtier-Polloth 2012). A different process, known as the Stöber method, is used to create stabilized suspensions spherical colloidal a-silica nanoparticles using controlled growth of particles following hydrolysis of alkylsilicates with condensation of silicic acid in an ethanolic solution with catalytic amounts of ammonia (Fruijtier-Polloth 2012, 2016).

Primary particles formed during the manufacture of synthetic a-silicas are in the nanometer range, but covalently bond during production to form indivisible SiO_2 aggregates >100 nm. These aggregates can further combine to form micron-sized agglomerates (Fruijtier-Polloth 2012, 2016; Merget et al. 2002; Taeger et al. 2016). With the exception of colloidal silica, primary nanosized particles do not exist in commercial products. However, colloidal dispersions have been shown to contain stable isolated nanoparticles in addition to aggregates in the respirable range (Fruijtier-Polloth 2012, 2016).

5.2.2 Import/Export

Chrystalline Silica. In 2012, 306,000 metric tons of industrial sand were imported into the United States and 4.36 million metric tons were exported. The largest quantities of industrial sand and gravel imported were from Canada (226,000 metric tons) and Mexico (64,000 metric tons) (USGS 2014b). The largest quantities of industrial sand and gravel exported were from the United States to Canada (2.33 million metric tons), Mexico (807,000 metric tons), and Japan (632,000 metric tons). In 2013, 160,000 metric tons of industrial sand were imported into the United States and 2.96 million metric tons were exported.

In 2013, 3 million metric tons of construction sand were imported into the United States (USGS 2015). The largest quantities of construction sand and gravel imported were from Canada (2.37 million metric tons), Mexico (210,000 metric tons), the Bahamas (150,000 metric tons), and other (270,000 metric tons).

Amorphous Silica. In 2014, 3,000 tons of diatomite were imported for use and 87,000 tons were exported (USGS 2015). Imports were from Mexico (1,080 metric tons), France (990 metric tons), China (300 metric tons), and others (630 metric tons). Several manufacturers reporting use of vitreous silica and

silica fume in 2015 indicated that the compound was imported; however, the imported volume was withheld (CDR 2017). Similarly, most manufacturing companies withheld export volumes; however, two companies reported 14,000 and 55,704 pounds of exported vitreous silica and one company reported 596,000 pounds of exported silica fume in 2015 (CDR 2017).

Import/export information on precipitated, pyrogenic, and gel a-silica compounds is available from the Chemical Data Reporting Submissions Database (CDR 2017). Several manufacturers reported use of imported precipitated, pyrogenic, and gel a-silica. Reported import volumes of 26,824–1,523,405 pounds were reported for precipitated a-silica by four manufacturers; however, most companies indicated that import volume data were confidential business information (CBI). For pyrogenic a-silica and a-silica gel, all imported volume data were withheld by manufacturers. Two manufacturers reported export volumes of 27,108 and 2,596,136 pounds for pyrogenic a-silica. Export volume data for precipitated a-silica and a-silica gel were either CBI or withheld.

Colloidal silica is imported primarily from Wales, with small amounts from Japan (amounts not reported). Exporting of colloidal silica is approximately 1,800 metric tons, primarily to Japan, Taiwan, and Canada, with some exports to Western Europe (Florke et al. 2008).

5.2.3 Use

Chrystalline Silica. Sand and gravel are used for road building and concrete construction (OSHA 2013c). In the United States, an estimated 44% of construction sand and gravel is used for concrete aggregates; the remainder is used for road base and coverings and road stabilization (25%), asphaltic concrete aggregates and other bituminous mixtures (13%), construction fill (12%), concrete products (1%), plaster and gunite sands (1%), snow and ice control (1%), and filtration, golf courses, railroad ballast, roofing granules, and other miscellaneous uses (3% combined) (USGS 2015).

Heavy industry uses quartz sand to produce high-temperature or refractory silica brick, foundry molds, and cores for the production of metal castings (IARC 2012). The oil and gas industry uses a water-sand mixture to fracture rock. Silica sand is used as a proppant, to prop open fractures and promote hydrocarbon flow and extraction. Water and proppants make up 98–99.5% of typical fracturing fluids. Silica sand with a round spherical shape and commonly graded particle distribution is specifically selected for hydraulic fracturing fluid production. Resin-coated silica is also used as a proppant (Holloway and Rudd 2014). In the United States, an estimated 72% was used as hydraulic fracturing sand

and well-packing and cementing sand; the remainder was used for glassmaking sand (13%), foundry sand (6%), whole-grain fillers and building products (3%), other whole-grain silica (2%), ground and unground sand for chemicals (2%), and other uses (2%) (USGS 2015). c-Silica is used as an asphalt filler and in bricks, mortar, plaster, caulk, roofing granules, wallboard, concrete, and dimension stone in building materials (IARC 2012). Quartz is used as filler in plastics, rubber, and paint or as an abrasive (e.g., blasting, scouring cleansers, sawing, and sanding). Quartz sand is used in municipal water filter beds and sewage treatment plants for filtering out impurities, sediment, and bacteria. Sand and gravel aggregates are used as abrasives on roads in winter (EC 2013).

c-Silica is used in products such as art clay, glazes, cleansers, cosmetics, pet litter, furniture foam, personal care products, talcum powder, and Jeweler's rouge (buffing agent) and as a gemstone (e.g., amethyst, citrine, and quartz) (IARC 2012; USGS 1992). Silica gemstones are used in jewelry, for collections, decorative art objects, and exhibits (USGS 2014a). Cristobalite sand, powder, and flour are used in the production of plastics, adhesives, wall paint, texture coatings, and road paint (Florke et al. 2008).

Quartz sand is used to manufacture glass and pure silicon for computer chips. Sand with >98% silica content is used for glass and ceramics. Finely ground c-silica is used to make ceramics (e.g., pottery, brick, and tile), porcelain, and fine china (IARC 2012; USGS 1992). Windows and specialized devices such as lasers use optical-grade quartz, while electronic-grade quartz is required for electronic circuits. Electronic-grade quartz crystal is used for accurate filters, frequency controls, and timers used in electronic circuits (USGS 2014b). Piezoelectric quartz crystals convert mechanical pressure into electricity and are used in advanced communication systems (IARC 2012; USGS 1992).

Silica stone, a type of c-silica, is produced to manufacture files, deburring-tumbling media, oilstones, and whetstones (USGS 2014b). Artificial, decorative stone products for bathroom and kitchen countertops are manufactured with up to 93% silica content (Kramer et al. 2012). Quartzite, tripoli, ganister, chert, and novaculite are commercially produced silica products (NTP 2014).

Tripoli is extremely fine-grained c-silica, used as a functional filler and extender in adhesives, plastics, rubber, and sealants, and in toothpaste, tooth polishing compounds, industrial soaps, metal- and jewelry-polishing compounds, and buffing and polishing compounds for lacquer finishing in the automobile industry (OSHA 2013c; USGS 2014b). Silica flour (CASRN 14808-60-7) is a fine grade of silica with particles up to 100 µm in diameter used in toothpaste, scouring powders, metal polishes, paints, rubber,

paper, plastics, wood fillers, cements, road surfacing materials, and foundry applications (NIOSH 1981; NTP 2009).

Amorphous Silica. Diatomite is used for removing microbial contaminants (e.g., bacteria, protozoa, and viruses) in public water systems (USGS 2015). In 2014, diatomite was used predominantly in filter aids (58%), absorbents (14%), cement (14%), and fillers (13%), and for other specialized applications such as pharmaceutical and biomedical uses (1%). Diatomaceous earth silica and silica gel are used as insecticides and acaricides to control insects, mites, and ticks (EPA 1991). The particle size of diatomaceous earth influences the insecticidal efficacy (Vayias et al. 2009). These compounds act as pesticide carriers and abrasive desiccants, which remove oily, protective films causing insects to dry out and die. Diatomite is applied to stored grain, food stores, feed, and ornamental plants, as well as on pets and their living or sleeping areas.

Silica fume, a-silica formed as a byproduct of silicon metal or ferrosilicon alloy production, is used in cement, concrete, and mortars to improve strength and durability (Florke et al. 2008). Transparent and nontransparent vitreous silica glass is used in tubing, rods, crucibles, dishes, boats, chromatographic substrate, precious-metal thermocouples protection, high temperature pyrometry prisms, lenses, cells, windows, other optical components, lasers, mercury vapor lamps, transducers, semiconductor technology, space shuttle windows, and optical fibers (Smith 2006).

Synthetic a-silicas, in particular silica gel compounds, are approved for use as food additives and in food packaging (FDA 2015a, 2015b; Fruijtier-Polloth 2012, 2016). The potential for a-silica migration into food from packaging will depend on the degree to which it is encapsulated into the packaging matrix (Stormer et al. 2017). They are also used as anti-caking agents and excipients in pharmaceuticals and dietary supplements (Fruijtier-Polloth 2012, 2016; IARC 1997; Merget et al. 2002). Silica gel is used as a desiccant and adsorbent for water and other species, thickener in dentifrice, matting agent in coatings, chromatographic media, and catalyst support (Florke et al. 2008; IARC 1997). Silica gel is also used as insecticides and acaricides to control insects, mites, and ticks (EPA 1991).

Various a-silica compounds are also used in cosmetics such as makeup preparations, hair dyes and colors, hair bleaches, hair straighteners, permanent waves, hair preparations, toothpaste, personal cleanliness products, skin care preparations, bubble baths, bath oils, tablets, and salts, body and hand preparations (excluding shaving preparations), moisturizing preparations, underarm deodorants, paste masks,

perfumes, foot powders and sprays, cleansing products, and suntan gels, creams, and liquids (Florke et al. 2008; Fruijtier-Polloth 2016).

Pyrogenic a-silicas are used in silicone rubber reinforcement, heat insulation, and as thickeners and anti-setting agents in liquid coatings, adhesives, inks and toners, undercoatings, and fire extinguishers (IARC 1997; Merget et al. 2002).

The primary use for colloidal silica is in investment casting (e.g., in production of jet engine components) (Florke et al. 2008). Colloidal silica can also be used in the production of refractory fibers, paper, and fibrous ceramics; to increase the strength and adhesion of paints and adhesives; for paper and cardboard frictionizing; as antisoil coating for carpets and other surfaces; and to polish silicon wafers (Florke et al. 2008; Lee and Kelly 1992). Colloidal silica can be used to increase the strength and adhesion of paints and adhesives (Florke et al. 2008). Beverages, including wine, beer, and fruit juices, can be clarified using colloidal silica (Florke et al. 2008).

5.2.4 Disposal

In the United States, approximately 34% of glass containers are recycled (USGS 2015). Foundry sand and cullet or glass pieces are also recycled, but to a lesser extent. Asphalt road surface layers, cement concrete surface layers, and concrete structures are recycled; however, it is considered to be a small percentage of aggregate (or total) amount used. Approximately 13.7 kg of Portland cement concrete was recycled in 2012 (USGS 2014c).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and

7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

There is no information on releases of silica to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Crystalline Silica. c-Silica may be released to air by natural and human processes. c-Silica is emitted into the ambient environment as a component of particulate emissions (EPA 1996). Process-stream air emissions of c-silica occur during activities, such as brick making, and fugitive emissions of c-silica occur ancillary to activities. For example, soil particles containing c-silica enter the atmosphere when vehicles travel on unpaved roads as fugitive emissions. Ambient dust containing silica by fugitive emissions include agricultural tilling, construction, mining, quarrying, hydraulic fracturing, paved and unpaved roads, and wind erosion sources. Soil geology factors are an important source of variability in c-silica emissions by fugitive releases in construction.

There are multiple possible sources of ambient c-silica. Industrial quarrying and mining are inherently dusty and are expected to contribute to ambient c-silica emissions (EPA 1996). c-Silica may be released during metallurgic manufacturing, although this is dependent on the c-silica use and application of particulate pollution control efforts. Power plant emissions contain c-silica from spent ash and combustion (EPA 1996). Sanding roads for deicing activities in winter may be a potential exposure route for c-silica as particulate emissions (EPA 1996).

Cristobalite dust may become released into the air by volcanic eruptions (OSHA 2013c). Forest fire and crop burning may release c-silica, as original a-silica in vegetation may release c-silica (cristobalite and quartz) when burned at high temperatures (EPA 1996). Wind erosion emissions of silica, where particulate aerosols are generated from air currents moving over soil, may spread c-silica particles in soils, and vary based on soil parameters, climatic factors, geographic features, vegetation type, and farming practices (EPA 1974).

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/m^3 for particles in the size range of 2.5–5 µm, as presented in Table 5-1 (EPA 1996). The mass median aerodynamic diameters (MMADs) of most c-silica particles released into the environment were >2.5 µm. Average ambient levels of c-silica with <15 µm 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 an annual average of 0.008 mg/m^3 (EPA 1996).

Table 5-1. Average Quartz Concentrations in Ambient Air for Sites in 22 U.S. Cities—Dichotomous Samples

		Coarse quartz (µg/m^{-3})		Fine quartz (µg/m^{-3})		TDM[a] (µg/m^{-3})		Quartz percentage of TDM[a]	
Site[b]	N[c]	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Coarse	Fine
Akron, OH	7	4.2	1.4	<0.1	0.1	71.2	16.1	5.9	<0.1
Boston, MA	1	8.0	–	0	–	140.8	–	5.7	0
Braidwood, IL	1	4.4	–	0	–	57.2	–	7.7	0
Buffalo, NY	14	2.3	1.4	0.1	0.3	83.6	26.6	2.8	0.1
Cincinnati, OH	2	2.6	1.5	0	–	63.2	1.0	4.1	0
Dallas, TX	4	2.6	1.0	0.3	0.3	62.7	22.9	4.2	0.5
El Paso, TX	10	2.2	1.1	0.1	0.1	76.5	43.2	2.9	0.1
Five Points, CA	3	6.6	3.2	1.0	1.2	124.8	84.1	5.3	0.8
Hartford, CT	2	3.0	2.1	0	–	54.8	6.2	5.5	0
Honolulu, HI	1	1.2	–	1.2	–	47.1	–	2.6	2.6
Inglenook, AL[d]	8	5.2	1.7	0.3	0.2	72.6	14.0	7.2	0.4
Kansas City, KS	8	4.7	2.6	0.4	0.4	69.2	28.3	6.8	0.6
Kansas City, MO	3	4.2	3.0	0.1	0.1	58.6	21.6	7.2	0.2
Minneapolis, MN	6	3.7	2.3	0.1	0.1	46.5	7.9	8.0	0.2
Portland, OR	7	1.4	0.6	<0.1	0.1	133.9	122.2	1.0	<0.1
Research Triangle Park, NC	3	0.9	0.5	0.4	0.1	37.0	3.5	2.4	0.1
Riverside, CA	4	3.0	1.1	0	–	106.6	42.2	2.8	0
St. Louis, MO	5	4.4	2.6	0.1	0.1	57.0	11.5	7.7	0.2
San Jose, CA	6	1.9	0.9	<0.1	0.1	67.0	27.3	2.8	<0.2
Seattle, WA	1	1.0	–	0.1	–	36.1	–	2.8	0.3

Table 5-1. Average Quartz Concentrations in Ambient Air for Sites in 22 U.S. Cities—Dichotomous Samples

		Coarse quartz ($\mu g/m^{-3}$)		Fine quartz ($\mu g/m^{-3}$)		TDM[a] ($\mu g/m^{-3}$)		Quartz percentage of TDM[a]	
Site[b]	N[c]	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Coarse	Fine
Tarrant, AL[d]	6	4.3	2.3	1.9	1.0	101.9	57.7	4.2	1.9
Winnemucca, NV	5	5.9	4.3	0.8	0.7	65.7	47.4	9.0	1.2

[a]Total dichotomous mass.
[b]Post office state abbreviations used.
[c]Number of filters analyzed.
[d]North Birmingham.

Source: EPA 1996

Green et al. (1990) evaluated agricultural particulate emissions and background emissions using regional historical data in Alberta, Canada. Variability was associated with the farm and the crops raised. Background total suspended particulate levels ranged from 0.040 to 0.080 mg/m^3, with 0.85–17.5% c-silica.

PM_{10} concentrations obtained 22–745 m downwind from a sand and gravel facility in California ranged from approximately 0.026 to 1.026 mg/m^3 (Shiraki and Holmen 2002). The airborne quartz mass concentrations from the three downwind sites ranged from 0.0262 to 0.0972 mg/m^3. Samples obtained at one site 1,495 m upwind had mass concentrations of quartz ranging from 0.0041 to 0.0163 mg/m^3.

In another study, the measured ambient concentrations of PM_4 c-silica ranged from below the detectable limit (0.0003 mg/m^3) to 0.0028 mg/m^3 in samples collected upwind and downwind of quarry and processing equipment at Carroll Canyon and Vernalis plants in California (Richards et al. 2009). The 8-hour working shift PM_{10} c-silica concentrations ranged from 0.001 to 0.0109 mg/m^3. The study was sponsored by the National Stone, Sand, & Gravel Association and samples were collected downwind of four crushing plants processing high-quartz-content rock (Richards et al. 2009).

Recent air monitoring reports conducted by the Minnesota Air Pollution Authority evaluated c-silica in PM_{10} and PM_4 particles in ambient air near industrial sand mining, processing, and transport sites (MPCA 2015a, 2015b). For PM_{10} particles, almost all measurements were below the detectable limits (0.001 mg/m^3), with all values <0.002 mg/m^3 (MPCA 2015a).

For PM_4 particles, almost all measurements were below the detectable limits (0.0012 mg/m^3), with all concentrations <0.007 mg/m^3 (MPCA 2015b). Air monitoring in downtown Winona, Minnesota showed that the c-silica concentration was <0.0005 mg/m^3 in all samples (MPCA 2015c).

Amorphous Silica. Data on a-silica releases into the air are limited, as most monitoring studies focus on c-silica (EPA 1996). a-Silica from diatomaceous earth can be released into the air at processing plants. Respirable dust concentrations for raw, calcined, and flux-calcined diatomaceous earth were reported to be <1.05, 0.21, and 0.14 mg/m^3, respectively, at a U.S. processing plant. c-Silica fraction of respirable dust was <1, 10–20, and 40–60%, respectively (IARC 1987). In a Swedish plant, respirable dust concentrations ranged from 0.1 to 2.0 mg/m^3, with c-silica fraction ranging from 5% in raw diatomite to 75% in calcined products (IARC 1987).

a-Silica byproducts may be released into the air due to releases of fly ash from power stations and various silicon manufacturing facilities (IARC 1997). In foundries and metallurgical industries that produce these byproducts (e.g., silica fume), the silica content of respirable dust ranged from 0.5 to 66 mg/m^3. Silica dust in these industries are primarily a-silica, but may contain up to approximately 20% c-silica (IARC 1987).

When crops (e.g., sugarcane) and non-crop vegetation are burned (e.g., forest fire), biogenic a-silica fibers are released. As discussed above, at high temperatures, burning vegetation may release c-silica (cristobalite and quartz) (EPA 1996; IARC 1997; Le Blond et al. 2010). Biogenic a-silica can also be released from sugarcane and rice crops during harvesting, transporting, and/or milling (IARC 1997).

According to the Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), synthetic a-silica, primarily precipitated and gel a-silica, may be released into the air in small amounts during the manufacturing process, at an estimated rate of 0.438 kt SiO_2/year. Total dust concentrations reported in a German synthetic pyrogenic a-silica plant were 2–7 mg/m^3 (IARC 1987).

5.3.2 Water

There is no information on releases of silica to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

c-Silica and biogenic a-silica particulates are naturally present in water as quartz and diatom fragments, with much higher levels of c-silica particulates compared with a-silica (IARC 1987, 1997; Trėguer and De La Rocha 2013). Silicon dissolves from minerals in water, forming bioavailable silicic acid, $Si(OH)_4$ (Lickiss 2006). c-Silica is virtually insoluble in water; however, dissolved silica flows from rivers and groundwater into the ocean where it may settle into marine sediments or be taken up by organisms as part of the biogeochemical silica cycle (Trėguer and De La Rocha 2013). a-Silica is poorly soluble, but as it is more soluble than c-silica (see Section 4.2), biogenic a-silica is the primary source of dissolved silica (Ning 2002). The term 'dissolved silica' (dSi) corresponds to silicic acid, which is formed from inorganic silicon dissolving from lithogenic sources, such as silicate minerals, as part of the weathering process. This weathering process is considered to be the greatest source of silica in aquatic ecosystems (Sferratore et al. 2006). The transformation and degradation of silica in water is further discussed in Section 5.4.2. Quartz sand is added to municipal water filter beds and sewage treatment plants for filtering out impurities, sediment, and bacteria (IARC 1987). According to the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), synthetic a-silica, primarily precipitated as gel a-silica, may be released into the water in small amounts during the manufacturing process, at an estimated rate of 2.1 kt SiO_2/year.

5.3.3 Soil

There is no information on releases of silica to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

Silica is a natural component of sediments, soils, and rock-forming minerals in magmatic and metamorphic rocks (Florke et al. 2008; IARC 1987, 1997). Quartz is present in trace to major amounts in sedimentary (e.g., sandstones and conglomerates) and metamorphic rock types (IARC 2012), and diatomite deposits are found worldwide (Florke et al. 2008). Silicon dioxide (diatomaceous earth) and silica gel are released to soil as registered pesticides for use on food and nonfood crops (EPA 1991). Biogenic a-silica is released into the soil after burning or natural decomposition of plants and crops (IARC 1997).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Quartz, cristobalite, and tridymite are found in rocks and soil and can be released to the environment through natural processes, such as weathering or volcanic eruptions, and from anthropogenic sources, such as foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth (IARC 2012). At least a trace amount of c-silica, in the form of quartz, is present in all soils (USGS 1992). Quartz is the major component of sand and dust particulate matter in air.

Both c- and a-silica particles may be transported by wind or water currents as part of the biogeochemical silica cycle. Dissolved silica is transported by river and groundwater sources into the ocean. Ocean water also contains silica from dissolution of terrestrial lithogenic silica in marine sediments, Aeolian dust settling on the ocean water surface, and weathering of continental rocks (Trėguer and De La Rocha 2013). a-Silica deposits may settle out of water into sediment from biogenic sources. c-Silica may undergo atmospheric transport as a fractional component of particulate emissions (EPA 1996).

5.4.2 Transformation and Degradation

Natural or synthetic changes in temperature and pressure may cause the crystalline structure of silica to change (IARC 2002). At elevated temperatures, the silica tetrahedron linkages break and reform into new crystalline structures (OSHA 2013c). Quartz, the most common form of c-silica, converts to cristobalite at 1,470°C, and cristobalite loses its crystalline structure and becomes amorphous fused silica at 1,723°C. The temperature-dependent transitions reverse at extremely slow rates. Different forms of silica co-exist after the heated silica crystal cools. At lower temperatures, the silica-oxygen bonds in the silica tetrahedron rotate or stretch, causing alpha and beta transitions that are readily and rapidly reversed upon cooling. Cristobalite and tridymite are formed when quartz or a-silica is subjected to extremely high temperatures (Leung et al. 2012; Mossman and Glenn 2013). Biogenic a-silicas are converted into cristobalite at approximately 800°C (IARC 1997). Cristobalite is produced when natural a-silica diatomaceous earth (diatomite) is heated with or without flux, resulting in cristobalite fractions of 10–20% in calcined product and 40–60% in flux calcined product (IARC 1987, 1997; OSHA 2013c).

Natural activities may cause silica polymorph transformations. For example, lightning strikes or meteorite impacts can change alpha quartz into keatite or coesite (IARC 2002), or vitreous silica (a-silica glass) may form under these conditions from the fusion of siliceous materials in soil (IARC 1997). Cristobalite may be produced by combustion metamorphism of naturally occurring substances (e.g., bituminous rocks, coal, or oil) (Clark and Peacor 1992). Anthropogenic activities may also cause transformation of silica from one polymorph into another (IARC 2012). Quartz in furnace bricks may convert to cristobalite when subjected to prolonged high temperatures. Burning of agricultural wastes, such as rice hulls, or forest fires may also cause a-silica to convert to cristobalite.

Air. Little information is available on the atmospheric reaction of silica. The c- and a-silica forms found in air as dusts are stable and not subject to photochemical reactions.

Water. Silicon dissolves from minerals in water forming bioavailable silicic acid ($Si(OH)_4$) reaching concentrations <2 mM at near neutral pH (Lickiss 2006). Silicic acid polymerization rate is dependent on temperature, ionic strength of the solution, pH, and silica saturation. Polymerization is fast in neutral and slightly alkaline solutions, and slow at pH values of 2–3 (Icopini 2005; Ning 2002). For example, silica polymerization rates were evaluated at 25°C in a series of controlled experiments. The reported fourth-order rate constants for the 0.01 molal ionic strength experiment with an initial concentration of 20.8 mmolal were 1.17×10^{-9} millimolal^{-3}·second^{-1} at pH 3 and 3.53×10^{-10} millimolal^{-3}·second^{-1} at pH 11 (Icopini 2005). Soluble silica half-lives were reported to be approximately 355 minutes at pH 6.5, 55 minutes at pH 8, and 95 minutes at pH 8.75 (Zuhl and Amjad 2013). a-Silica is more soluble than c-silica; therefore, the primary source of dissolved silica in natural waters is biogenic a-silica (Ning 2002). The portions of c-silica and biogenic a-silica that do not dissolve settle into the sediment. Cycling between silica particles and dissolved silica occurs at the sediment-water interface (Tréguer and De La Rocha 2013; Tréguer et al. 1995). Additionally, dissolved silica is a source of biogenic a-silica for diatoms, radiolarians, and sponges (IARC 1997). Colloidal silica is non-reactive and stable in fresh water, but can be depolymerized in seawater; polymerized colloidal silica settles into the sediment (Ning 2002).

Sediment and Soil. Quartz is extremely resistant to physical and chemical breakdown by the weathering process (USGS 1992). The weathering rate of a square meter of catchment area from different geographic areas using field measurements is 10^{-2}–10^{-1} moles·m^{-2}·year^{-1} (Ning 2002). Synthetic a-silica compounds are inert, and are not expected to transform or degrade in soil (ECETOC 2006). Terrestrial plants uptake bioavailable forms of a-silica from the soil, particularly grasses (IARC 1997).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to silica depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of silica in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on silica levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-2 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-3.

Table 5-2. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air (dust)	c- or a-silica: 5 µg/sample	NIOSH 2003a, 2003c, 2003d
Water (dissolved silica)	10 µg silica/L	EPA 2003; USGS 1987
Soil/sediment	Quartz: <1% of sample or 8 µg/sample	Barredo and Polo Diez 1980; Sheffield 1994; Stopford 1994
Biological samples	c-silica: 10 µg/sample	NIOSH 2003b

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-3. Summary of Environmental Levels of Silica

Media	Low	High	Reference
Outdoor air	Urban: c-Silica (0.3–10.5 µM): 0.25 µg/m^3	Urban: c-Silica (0.3–10.5 µM): 2.87 µg/m^3	Bhagia 2009; De Berardis et al. 2007; ECETOC 2006; IARC 1997; Lawson et al. 1995
	Near industrial site: Quartz: 41.07 µg/m^3	Near industrial site: Quartz: 57.22 µg/m^3	
	5 km from industrial site: Quartz:3.51 µg/m^3	5 km from industrial site: Quartz: 3.51 µg/m^3	
	Ambient a-silica: <0.2 µg/m^3	Ambient a-silica: 135 µg/m^3	
	a-Silica near farming operation: <0.004 fibres/mL	a-Silica near farming operation: 0.2 fibres/mL	

Table 5-3. Summary of Environmental Levels of Silica

Media	Low	High	Reference
Indoor air	Near stone crushing site: PM_4=500 µg/m^3 (7–24% c-silica; ~35–120 µg/m^3)	Near stone crushing site: PM_4=650 µg/m^3 (7–24% c-silica; ~46–156 µg/m^3)	Mukhopadhyay et al. 2011
Surface water	Dissolved silica: 0.12 mg/L	Dissolved silica: 6 mg/L	Tréguer et al. 1995
Deep water	Dissolved silica: 0.6 mg/L	Dissolved silica: 10.8 mg/L	Tréguer et al. 1995
Ground water	Dissolved silica: 17 mg/L	Dissolved silica: 17 mg/L	Tréguer et al. 1995
Drinking water	3.3 mg/L	7.1 mg/L	ECETOC 2006; Sferratore et al. 2006
Food (ppb)	Estimated a-silica intake from food: 0.28 mg/kg/day	Estimated a-silica intake from food: 12.7 mg/kg/day	Fruijtier-Polloth 2016
Soil	c-silica: trace a-silica: 3.9 mg/g a-silica: 706 g/kg (dry weight)	c-silica: 95% a-silica: 5.2 mg/g a-silica: 706 g/kg (dry weight)	ECETOC 2006; NTP 2014; Sferratore et al. 2006; USGS 1992

No data are available on levels of silica in air, water, and soil at NPL sites (ATSDR 2017).

5.5.1 Air

Crystalline Silica. Widespread natural occurrence and use of silica-containing materials result in silica-containing airborne dusts being present in the environment (Moore 1999). Silica particles suspended in the air create non-explosive dusts (OSHA 2013c). Silica from unconsolidated material on the earth's surface in the form of soils, deserts and beaches, volcanic ash, and extraterrestrial dust are natural sources of silica in air (Moore 1999). Remote continental air contains a background gravimetric airborne dust concentration of 0.04 mg/m^3, of which ≥10% is c-silica. Desert dust consists of fine particles (<10 µm) of quartz (IARC 1997).

Samples collected from an urban area in Rome, Italy between September 2004 and October 2005 were analyzed to determine the concentration of silica particles in the inhalable particulate fraction (De Berardis et al. 2007). The total PM10 particulate in the samples contained 1.6±0.6–10.4±1.4% silica or 0.00025–0.00287 mg c-silica/m^3 air. The silica particles in the samples had a mean diameter range of 0.3–10.5 µm, and >87% had a diameter of <2.5 µm. The authors hypothesized that Southern winds from the Sahara Desert carry silica particles into Mediterranean Europe. Corresponding data on the intensity and direction of the wind, humidity, and rain on and near sampling days demonstrated a strong relationship between the concentration of c-silica in the samples and meteorological-climate conditions. The weight percent of c-silica in particles was higher between April and June than the winter months.

The concentration of quartz was reported to be ≤0.034 mg/m^3 in air samples from Tokyo in 1965. The concentration of cristobalite and potential sources of airborne silica were not reported (NTP 2009). Dust samples collected from two communes in a sandy area of Gansu Province, China during the windy season ranged from 8.35 to 22 mg/m^3. The dust consisted of fine particles (<5 µm) with a free silica content of 15–26% (IARC 1997).

Volcanic ash collected at 34–36 km altitude from El Chichón (Mexico) were composed of 35% cristobalite and keatite. Volcanic ash collected from Mount St. Helens in Washington State contained 3–7% c-silica (IARC 1997).

Air monitoring was performed using PM_{10} high volume samplers at two locations near an industrial slate pencil site and at one control site 5 km away (Bhagia 2009). The quartz concentrations were 0.04107±0.02125–0.05722±0.02205 mg/m^3 near the slate industrial site and 0.00351±0.00145 mg/m^3 at the control site. In another study, PM_{10}, $PM_{4,}$ and $PM_{2.5}$ ambient air samples were obtained for indoor air in two villages neighboring stone crushing sites in India (Mukhopadhyay et al. 2011). The silica content in the samples was between 7 and 24%. The average ambient PM_{10} values in the two neighboring communities were 0.77 and 0.46 mg/m^3. The indoor air average PM_4 values were 0.5 and 0.65 mg/m^3, respectively, and the $PM_{2.5}$ values were 0.13 and 0.28 mg/m^3, respectively. The workers' average exposure to respirable particulates (PM_4) in three stone crushing units ranged from 4.51 to 8.15 mg/m^3 (Mukhopadhyay et al. 2011).

Amorphous Silica. According to the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), ambient a-silica levels in the air range from <0.2 to 135 µg/m^3. In California, 1 of 11 samples obtained upwind of rice farming operations and half of the downwind samples contained a-silica at a concentration of 0.02 fibers/mL; the overall mean concentration of all downwind samples was 0.004 fibers/mL. Silica fibers (fiber length in the respirable dust fraction: >5 µm, with 90% of fibers <5 µm in length; range of fiber width: 0.2–75 µm), measured by polycarbonate membrane filter, were detected in 4 of 14 samples in neighboring towns on days when there was rice burning at a mean concentration of <0.004 fibers/mL (Lawson et al. 1995). a-Silica fibers were identified in three of seven smoke samples collected near burning sugarcane fields in Hawaii (IARC 1997).

5.5.2 Water

Silicon dissolves from natural sources of c- and a-silica in water, forming bioavailable silicic acid, $Si(OH)_4$, reaching concentrations up to 2 mM at near neutral pH (Lickiss 2006). a-Silica is more soluble than c-silica (see Section 4.2); therefore, the primary source of dissolved silica is biogenic a-silica (Ning 2002). Ning (2002) reported typical concentrations of silica in natural waters of 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). Tréguer et al. (1995) reported average dissolved silica concentrations of 9 mg/L in rivers, 4 mg/L in lakes, and 17 mg/L in groundwater. The average reported concentration of dissolved silica in ocean waters, nearly exclusively in monosilicic acid form, was 4.2 mg/L, with low concentration at the surface (0.12–6 mg/L) and higher concentrations in deep and bottom waters (0.6–10.8 mg/L) (Tréguer et al. 1995).

Median seasonal concentrations of silica were reported for 12 sites in the Hudson River Basin in New York State (Wall et al. 1998). The samples taken between December and March had silica concentrations ranging from 2.8 to 10.0 mg/L. The samples collected between April and November had silica concentrations ranging from 0.72 to 9.1 mg/L. George et al. (2000) measured the total silica content in springs and wells in Southern Nevada. Total silica concentrations were detected for the low molecular weight silica that were not colloidal. The authors suggested that decreases in the silica concentration was due to biological causes, such as phytoplankton uptake, based on silica concentrations correlating to the nitrate concentration trend.

According to the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), U.S. drinking water contains a median dissolved silica concentration of 7.1 mg/L. In the Seine River watershed, the average a-silica concentration in tap water and two water treatment plants was 4.1 mg/L (Sferratore et al. 2006).

5.5.3 Sediment and Soil

Crystalline Silica. Silica is ubiquitous in the environment; over 95% of the earth's crust is made of silica-containing minerals and c-silica (Uhrlandt 2006). c-Silica has been found in samples from every geologic era and from every location around the globe (USGS 1992). Alpha quartz is most common in nature, accounting for almost 12% by volume of the earth's crust (OSHA 2013c). At least a trace amount of c-silica, in the form of quartz, is present in all soils. Quartz is found as crystals, aggregates, or discrete

particles (IARC 1997). The silica polymorphs, cristobalite and tridymite, are found in rocks, soil, and volcanic rocks. Volcanic rocks in California and Colorado are a major source of cristobalite and tridymite in the United States (NIOSH 1986). The c-silica polymorphs keatite, coesite, stishovite, and moganite are rarely found in nature (IARC 2012).

Quartz is an important component of many igneous and sedimentary rocks (IARC 1997). The sedimentary rocks sandstones, greywackes, and shales contain 82, 37, and 20% quartz by weight, respectively. Some of the igneous rocks that contain quartz are rhyolites, alkali granites, alkali rhyolites, and granites in 33.2, 32.2, 31.1, and 29.2% quartz by weight, respectively. Typically, silica sand deposits have a silica content of 95%, although impurities may reach up to 25% (NTP 2014).

Soils from North Carolina were analyzed for quartz content (Stopford and Stopford 1995). Sandy-loam soils with particles in the 4.25 µm fraction had an average quartz content of 15.2%, clay soils had 2.2%, and sandy soils had 31.6%. Quartz was detected in dust samples collected from indoor and outdoor locations in Oman (Abdul-Wahab et al. 2005). Samples obtained inside and outside a residential house in Al-Suwayq (Oman) contained quartz, dolomite, and gypsum. Calcite, quartz, dolomite, and goethite were detected in samples obtained in a residential house near a cement plant.

Settled dust collected from five family farms located in Lublin, Jastków, Konopnica, and Niemce, Poland contained 0.7–65.2% silica (Molocznik 2002). Average free silica content in bituminous coal was 174,000 ppm (standard deviation 94,000) from Xuan Wei, China and 18,000 ppm (standard deviation 17,000) from the United States (Large et al. 2009). Grainsize analysis of coal from Xuan Wei, China indicates that 35–55% of the total quartz had a particle size <10 µm.

Ash from the Eyjafjallajökull Volcano eruption in 2010 and from the eruption of Grímsvötn, Iceland in 2011 was studied and compared to ash from Soufrière Hills Volcano, Montserrat that has been studied since eruptive activity began in 1995 (Horwell et al. 2013). Ash from Eyjafjallajökull had a c-silica abundance of 1.4–3.2 weight % and ash from Grímsvötn did not have detectable c-silica content. Ash samples from Soufrière Hills contained 5.2–15.2 weight % cristobalite and 1.2–1.6 weight % quartz (Horwell et al. 2010). c-Silica is formed in volcanic environments by lava dome eruptions with viscous, silicic magma extruded from the volcano at approximately 800°C, forming a dome of rock in the crater (Horwell et al. 2012).

Amorphous Silica. According to the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), a-silica levels in soil and sediment were approximately 706 and 524 g/kg (dry weight). In the Seine River watershed, mean a-silica mean concentrations were 5.2, 4.7, and 3.9 mg Si/g in cultivated soil, meadow, and forest, respectively. Suspended matter from the winter and summer had a-silica average concentrations of 5.7±0.9 and 18.4 mg Si/g (Sferratore et al. 2006).

5.5.4 Other Media

Organisms, such as diatoms and radiolarian, build up exoskeletons of hydrated a-silica from silicic acid in water. Plants use silicic acid to make a-silica materials for strengthened stems and leaves or protective spikes (Ning 2002). a-Silica also accumulates in rice, millet, sugarcane, and wheat plants (Rabovsky 1995). Liu et al. (1996a) measured free silica content of rice husk ash to be 91.4% (25.5% cristobalite and 3.6% tridymite) when the rice husk was burned at 1,100°C; however, the silica content was dependent on the temperature of burning. When the rice husk was burned at 350°C, the ash contained 23% free silica, of which 1.1% was quartz, 3.4% was cristobalite, and 0.5% was tridymite. Tridymite is rarely reported in the workplace or found in nature (Smith 1998).

Le Blond et al. (2010) reported raw air dried sugarcane leaf silica concentrations ranging between 0.45 and 1.8 weight %. Sugarcane trash ash burned at temperatures up to 1,056°C had silica concentrations ranging from 10.38 to 24.77 weight %. Bagasse, the fibrous remains left after sucrose extraction, is often burned as an energy source. The bagasse ash contained between 39.2 and 40.0 weight % silica content. No c-silica was found in the ash burned at temperatures <800°C; however, cristobalite and quartz formed when the sugarcane burned at higher temperatures.

High-purity, mesoporous a-silica was found in a study of the freshwater sponge, *Cauxi*. The study evaluated the skeleton and spicules of a sample made of glassy silica with a length of 305±18 and a width of 15.6±1.5 μm (Jensen et al. 2009). An axial filament that is known to contain the silica catalyst protein, silicatein α, was also evaluated.

5.6 GENERAL POPULATION EXPOSURE

Crystalline Silica. c-Silica is ubiquitous in the environment. Over 95% of the earth's crust is made of silica-containing minerals and c-silica (Uhrlandt 2006). As silica is part of the natural environment and

widely distributed in soils and rocks, predominantly as quartz, exposure to c-silica is unavoidable (IARC 1997). c-Silica exposure is expected in both occupational and general settings from the natural environment and consumer use of products containing c-silica (NTP 2014; USGS 1992). It is important to consider the form and availability of silica when discussing silica exposure because silica has multiple forms, particle sizes, surface areas, and surface chemistry (OSHA 2013c). Inhalation is expected to be the primary route of exposure to c-silica for the general population from the use of commercial products containing quartz (IARC 2012). Occupational exposure to c-silica is further discussed in Section 5.7, Populations with Potentially High Exposures.

c-Silica is an established air contaminant. Local meteorological conditions can give rise to silica-containing dust, most notably in areas around recent volcanic eruptions, mine dumps, and deserts (e.g., sand storms) (IARC 1987, 1997). People who live near quarries, sand or gravel operations, or hydraulic fracturing operations may be exposed to respirable c-silica. Consumer exposure to respirable c-silica is possible from the use of abrasives, sand paper, detergent, grouts, and concrete (IARC 1997). Diatomaceous earth is used as a filler in reconstituted tobacco sheets and may be converted to cristobalite at high temperatures when passing through the burning tip of tobacco products (IARC 1987).

Dermal and oral exposure to quartz may occur through the use of consumer and commercial products, including cleansers, skin care products and soaps, art clays and glazes, pet litter, talcum powder, caulk, pharmaceuticals, putty, paint, and mortar (NTP 2009). A homeopathic remedy called silicea, prepared from flint, quartz, sandstone, and other rocks, is another potential source of dermal silica exposure. Although quantitative data are not available, ingestion of potable water containing quartz particles is a potential source of exposure for the general population (IARC 2012).

Amorphous Silica. As with c-silica, a-silica is widespread in nature. Biogenic forms are found in diatomaceous earth and various plant life, particularly grasses, which release a-silica into the soil through burning or normal decay. Non-biogenic forms are found in volcanic glass (IARC 1997).

Inhalation is the primary source of concern for occupational exposure to a-silica. Diatomaceous earth miners and sugarcane and rice farmers may be exposed to natural sources of a-silica. Workers involved in ferrosilicon industrial processes and workers that produce or use synthetic a-silica products may also be exposed (IARC 1997). Occupational exposure to a-silica is further discussed in Section 5.7, Populations with Potentially High Exposures.

People who live near power stations and various silicon manufacturing facilities may be exposed to a-silica (and c-silica) via fly ash release. Additionally, people living near sugarcane and rice farms may be exposed to elevated air levels of biogenic a-silica fibers (IARC 1997).

Exposure to a-silica may occur through dietary intake based on the widespread use of synthetic a-silica compounds in the food, cosmetics, and pharmaceutical industries as anticaking agents or carriers. Specifically, synthetic a-silica used in food packaging is expected to be an important source of exposure (FDA 2015a, 2015b). The potential for migration into food will depend on the degree to which it is encapsulated into the packaging matrix (Bott et al. 2015; Stormer et al. 2017). The average daily intake of a-silica from food ranges from 0.28 to 12.7 mg/kg/day, with dietary supplements delivering doses up to 700 mg/day (Fruijtier-Polloth 2016). According to the European Centre for Ecotoxicology and Toxicology of Chemicals Joint Assessment of Commodity Chemicals report (ECETOC 2006), U.S. drinking water contains a median dissolved silica concentration of 7.1 mg/L. In the Seine River watershed, the average a-silica concentration in tap water and two water treatment plants was 4.1 mg/L (Sferratore et al. 2006). Although quantitative data are not available, diatomite fragments are present in drinking water worldwide, and are a potential source of exposure for the general population (IARC 1997).

Exposure to a-silica may occur through use of silicon dioxide (diatomaceous earth) and silica gel pesticides to control insects and arachnids in stored grain crops, food handling areas, hospitals, and sewage systems; on animals/pets; or in living quarters (EPA 1991).

Dermal exposure to a-silica may occur through contact with use of consumer and commercial products, including cosmetics (e.g., makeup, hair products, toothpaste, personal cleanliness and bath products, skin care products, underarm deodorants, perfumes, foot powders and sprays), paints and adhesives, and silica gel pesticide products (EPA 1991; Florke et al. 2008; Fruijtier-Polloth 2016; Merget et al. 2002).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational Exposure to Crystalline Silica. Respirable c-silica is extremely common, is widely used in materials and products, and is naturally occurring; therefore, occupational exposures occur in a variety of industries and occupations (NIOSH 2002). Metal, nonmetal, and coal mines and mills, granite quarrying and processing sites, hydraulic fracturing operations, crushed-stone industries, foundries, ceramics, construction, and sandblasting operations are most frequently found to have respirable quartz levels >0.1 mg/m^3 (NTP 2014). Main industries where c-silica exposure is likely are those that require job

activities involving the movement of earth, disturbing products containing silica, and handling or use of sand and other silica-containing products (IARC 1997, 2012). Workers in other industries also have reported exposure to silica, including shipbuilding and repair, rubber and plastics, paint, soap and cosmetics, roofing asphalt and felt, agricultural chemicals, jewelry, arts, crafts, sculpture, counter manufacture and installation, dental material, boiler scaling, and automobile repair (NIOSH 2002).

A total of 81,221 workers had the potential to be exposed to quartz at 4,077 facilities in 59 industries in 1972–1974 based on data from a National Occupational Hazard Survey conducted from 1972 to 1974 (NTP 2014). The survey for 1981–1983 reported that 944,731 workers (112,888 women) were potentially exposed to quartz and 31,369 workers (2,228 were women) were potentially exposed to cristobalite (NTP 2014). NIOSH estimated that approximately 1.7 million workers had the potential to be exposed to respirable c-silica based on data from 1986, of which 722,708 workers were in mining industries and 522,748 workers were in non-mining industries (NIOSH 2002).

Yassin et al. (2005) estimated that 119,381 workers in the United States are potentially exposed to high levels of c-silica based on data from 7,209 personal sample measurements collected from 1988 to 2003 stored in the OSHA Integrated Management Information System (IMIS) database. Geometric mean airborne silica exposure levels among workers were 0.070 mg/m^3 from 1988 to 1991, 0.068 mg/m^3 from 1992 to 1995, 0.080 mg/m^3 from 1996 to 1999, and 0.073 mg/m^3 from 2000 to 2003. Freeman and Grossman (1995) evaluated data for measured respirable quartz in 1,655 inspections from 255 industries collected by OSHA. The most severe 8-hour TWA exposures were in the fabricated structural metal and painting and paper hanging industries.

Radnoff et al. (2014) evaluated the occupational exposure of workers in Alberta, Canada to respirable quartz. Workers in the oil and gas industry had the highest maximum exposure of 8.6 mg/m^3; however, workers in the sand and mineral processing industry had the highest geometric mean exposure to quartz at 0.09 mg/m^3. Bricklayer and concrete job activities (coring, cutting, or finishing) had a geometric mean exposure concentration of 0.105 mg/m^3 respirable quartz exposure, which was the highest among the occupations in the study. In Italy, geometric mean occupational exposure to respirable c-silica concentrations ranged from 0.007 mg/m^3 for workers in the manufacture of basic metals to 0.045 mg/m^3 for construction workers (Scarselli et al. 2014).

Agricultural workers in the United States may be exposed to dust containing a significant percentage of respirable c-silica (Linch et al. 1998). In agriculture operations, plowing, harvesting, using machinery,

burning agricultural waste, and processing agricultural products are possible routes of silica exposure from the soil (NIOSH 2002). Farmers may be exposed to cristobalite (and a-silica) during crop burning or incineration (Rabovsky 1995). Agricultural workers from 10 farms in Yolo and Solano counties in California wore personal sampling equipment to measure exposure to inhalable and respirable dust levels (Nieuwenhuijsen et al. 1999). The geometric mean concentration of respirable dust ranged from 0.05 to 2.83 mg/m^3 (the dust contained 18.6% c-silica). Inhalable dust concentrations ranged from 0.30 to 45.14 mg/m^3 and contained 7.4% c-silica overall. Respirable silica concentrations were measured for farm workers in eastern North Carolina (Archer et al. 2002). The mean silica concentrations ranged from below the level of detection (0.005 mg/m^3 quartz) to 3.91±2.31 mg/m^3 for sweet potato planting in Wayne County.

Respirable quartz concentrations were measured at three South African farms with either sandy, sandy loam, or clay soil (Swanepoel et al. 2011). The geometric mean respirable quartz concentrations were 0.0317, 0.0316, and 0.031 mg/m^3 for the sandy soil, sandy loam soil, and clay soil farms, respectively. The level of silica in air collected from five family farms located in Lublin, Jastków, Konopnica, and Niemce, Poland contained 1.1–22% silica (Molocznik 2002).

Industrial hygiene practices such as engineering controls, tailored work practices, respirators, and worker training can be used to minimize potential silica health hazards. In the construction industry, wet cutting using water to control airborne dust levels and vacuum dust collection are used to reduce silica dust exposure (OSHA 2009). Construction workers may become exposed to silica from sand, concrete, rock, soil, mortar, plaster, and shingles (NIOSH 2002). In ‘new’ construction, concentrations of respirable c-silica range from 0.013 to 1 mg/m^3 (Radnoff et al. 2014). In the United States, a study evaluated silica exposure at 36 construction sites (Rappaport et al. 2003). The highest exposures, with a median silica concentration of 1.28 mg/m^3, were from painters, followed by laborers at 0.350 mg/m^3, bricklayers at 0.320 mg/m^3, and operating engineers at 0.075 mg/m^3. Quartz dust geometric mean concentrations ranged from 0.01 mg/m^3 (geometric standard deviation of 2.6) to 0.61 mg/m^3 (geometric standard deviation of 5.4) for the tuck point grinder job in a personal silica exposure monitoring data study of the construction industry (Flanagan et al. 2006).

Abrasive blasting is considered to be one of the more hazardous operations involving silica, and it is important for workers performing this task to use proper respiratory protection (Madl et al. 2008). A study was performed to evaluate 11,845 measurements obtained for exposure to respirable c-silica in the construction industry (Beaudry et al. 2013). The majority of the measurements (92%) were obtained with

personal measurement devices from 1974 to 2009. The highest geometric mean concentration of c-silica that workers were exposed to was 1.59 mg/m^3 for the abrasive blasting task. In New Jersey, occupational exposure monitoring was performed for a footbridge repainting project using a substitute abrasive with no to low abrasive content in 2002 (Meeker et al. 2005). The workers' exposures to respirable silica were still high, most likely because a high level of silica contaminant, ranging from 0.52 to 25.66 mg/m^3, was found in the surface paint. Personal samples for exposure to quartz were collected on heavy and highway construction workers (Woskie et al. 2002). The geometric mean concentration for respirable quartz ranged from 0.007 to 0.026 mg/m^3 for the job tasks of operating engineers and laborers, respectively. Personal breathing zone air samples were collected to analyze home construction roof workers' exposure to c-silica (Hall et al. 2013). The 8-hour respirable dust concentration ranged from 0.2 to 3.6 mg/m^3. The respirable silica 8-hour exposures ranged from 0.04 to 0.44 mg/m^3. The geometric mean concentrations of respirable silica were 0.12, 0.14, 0.16, and 0.14 mg/m^3 for four companies.

Granite and marble countertop workers had 8-hour TWA exposures as high as 3.07 mg/m^3 (14% quartz) in a 1999 OSHA inspection and 7.4 mg/m^3 (0.7% quartz) based on personal monitoring data (Fairfax and Oberbeck 2008). Akbar-Khanzadeh et al. (2007) measured the concentration of c-silica dust and respirable particulate matter encountered during indoor concrete grinding, wet grinding, and ventilated grinding and uncontrolled conventional grinding. The mean TWA c-silica dust concentrations with no general ventilation were 86.0 mg/m^3 for uncontrolled grinding, 1.40 mg/m^3 for wet grinding, and 0.161 mg/m^3 for local exhaust ventilation grinding; when general ventilation was used, the dust concentrations were 25.4 mg/m^3 for uncontrolled grinding, 0.521 mg/m^3 for wet grinding, and 0.148 mg/m^3 for local exhaust ventilation grinding. c-Silica dust mean concentrations during surface concrete grinding with a 100–125 mm grinding cup were 0.17 and 0.11 mg/m^3 with a HEPA-cyclone and HEPA tank, 0.54 and 0.12 mg/m^3 with a shop vacuum, 0.96 and 0.27 mg/m^3 with wet grinding, and 23.6 and 5.78 mg/m^3 with and without general ventilation, respectively (Akbar-Khanzadeh 2010). When a 180-mm cup was used, the silica dust concentrations were 0.54 and 0.20 mg/m^3 with a HEPA-cyclone and HEPA tank, 1.90 and 0.14 mg/m^3 with a shop vacuum, 8.83 and 2.08 mg/m^3 with wet grinding, and 55.3 and 15.1 mg/m^3 with and without general ventilation, respectively.

The mean exposure to respirable dust and quartz was reported for the Dutch construction industry (van Deurssen et al. 2014). The overall mean concentrations were 0.88 mg/m^3 for respirable dust and 0.10 mg/m^3 for quartz. The concentrations ranged from 0.02 to 33.76 mg/m^3 for respirable dust and from 0.01 to 1.36 mg/m^3 for quartz.

Workers in the nonmetal mining operations (i.e., sandstone, clay, shale, and miscellaneous nonmetallic mineral mills) had higher exposure to silica dust than those in metal mining operations. Baggers, general laborers, and personnel involved in the crushing, grinding, and sizing operations had the highest exposure within the mills (IARC 1987). In samples obtained from metal and nonmetal mines from 2005 to 2010, the respirable dust geometric mean concentrations were highest in underground nonmetal and limestone mining samples at 0.88 and 0.73 mg/m^3, with quartz present in 0.029 and 0.024 mg/m^3, respectively (Watts et al. 2012). The highest geometric mean quartz concentration was found in underground sand and gravel mines at 0.068 mg/m^3.

In a cohort mortality study of North American industrial sand workers, the overall geometric mean exposure to respirable c-silica was calculated to be 0.042 mg/m^3 based on 14,249 measurements taken between 1974 and 1998 (Rando et al. 2001). Granite shed workers in Elberton, Georgia were exposed to respirable c-silica at a mean exposure concentration of 0.052 mg/m^3 (Wickman and Middendorf 2002). Exposure surveys were conducted in a granite quarry with side-by-side arrays of four closed-face cassettes, four cyclones, four personal environmental monitors, and a real-time particle counter (Sirianni et al. 2008). c-Silica concentrations ranged from 0.41 mg/m^3 from a personal exposure monitor to 12.38 mg/m^3 for a closed-face cassette. Differences were reported related to the size and silica content of airborne particles depending on the tools being used and the granite activity level at the time of sampling.

In a c-silica occupational exposure study performed in the United States, a geometric mean of 0.065 mg/m^3 was reported for all occupations in the stonework masonry industry based on data collected between 1988 and 2003 (Yassin et al. 2005). A study evaluating the occupational exposure for workers at 18 silica sand plants from 1974 to 1996 from 4,269 respirable dust samples, reported a geometric mean quartz concentration of 25.9 mg/m^3 (geometric standard deviation of 10.9), and samples ranged from <1 to 11,700 mg/m^3 (Sanderson 2000).

An average concentration of 0.22 mg/m^3 was reported for 148 carvers at a stone-carving company in Thailand (Yingratanasuk et al. 2002). Pestle makers and mortar makers had exposure to c-silica at concentrations of 0.05 and 0.88 mg/m^3, respectively. Personal sampling by workers in a small-scale mining operation reported 15.5 mg/m^3 respirable dust, 2.4 mg/m^3 respirable c-silica, 1.5 mg/m^3 respirable combustible dust, and 28.4 mg/m^3 ‘total’ dust during activities such as drilling, blasting, and shoveling (Bratveit et al. 2003). Respirable dust and respirable c-silica were 4.3 and 1.1 mg/m^3, respectively, during shoveling and loading of sacks. An overall geometric mean of 0.09 mg/m^3 of respirable c-silica was

reported from samples collected at seven U.K. quarries between 1978 and 2000 (Brown and Rushton 2005a).

Occupational exposure of coal miners to respirable coal mine dust in the United States was evaluated using data collected from 1995 to 2008 (Joy 2012). Quartz content in airborne dust was variable, and >5% quartz content was found in 20,193 samples (21.6%) below the 0.100 mg/m^3 respirable dust standard. Average respirable quartz exposure concentrations for miners at surface coal mines in the United States ranged from 0.08 mg/m^3 in 1986 to 0.15 mg/m^3 in 1982 based on data from the Mine Safety and Health Administration (MSHA) inspectors (Piacitelli et al. 1990).

Average exposure was calculated using MSHA compliance data from 16,578 measurements at 4,726 mines obtained from 1998 to 2002 (Weeks and Rose 2006). Continuous miner operators were exposed to a mean concentration range of 0.0061–0.2717 mg/m^3. Workers in underground mines had the highest geometric mean concentration of 0.050 mg/m^3. Workers in strip and open pit mines and mills or preparation plants had slightly lower mean concentrations of 0.047 and 0.045 mg/m^3, respectively.

The overall geometric mean concentration of respirable c-silica was 0.027 mg/m^3 for underground coal mining in the United Republic of Tanzania (Mamuya et al. 2006). Employees for the development team, mine team, transport team, and maintenance team reported geometric mean concentrations of 0.073, 0.013, 0.006, and 0.016 mg/m^3, respectively. A study evaluating respirable samples for silica exposure from two copper mines in Mufulira and Nkana, Zambia reported concentrations of 0.143±0.2 and 0.060±0.06 mg/m^3 of respirable quartz, respectively (Hayumbu 2008). The mean respirable quartz concentration reported in Ontario gold mines ranged from 0.02 mg/m^3 for the task operations designated as other to 0.17 mg/m^3 for the conveying and transporting operations (Verma et al. 2014). The highest (or maximum) concentration reported was 0.85 mg/m^3 for the Conveying and Transporting task.

Personal respirable dust exposures were collected at crushed stone facilities in the United States (Kullman et al. 1995). Workers with limestone were exposed to dust with an 11% mean α-quartz content or a geometric mean concentration of 0.04 mg/m^3 (standard deviation 1.88). Workers with granite were exposed to dust with 37% mean α-quartz content or a geometric mean concentration of 0.06 mg/m^3 (standard deviation 1.94). Workers with Traprock were exposed to dust with 15% mean α-quartz content or a geometric mean concentration of 0.04 mg/m^3 (standard deviation 1.62). Silica flour is made by drying and milling mined quartz into fine particles, many of which are respirable (MMWR 1989). The MSHA measured respirable quartz exposures at 28 plants using personal breathing-zone air samplers and

found free silica levels above the MSHA permissible exposure limit (PEL) of 0.1 mg/m^3 in 52% of the samples.

Exposure levels to airborne respirable dust with quartz powder sizes of 1.52–3.04 or 3.04–6.08 mm in quartz manufacturing units in India were studied (Fulekar 1999). The mean respirable dust exposure level was 2.93 mg/m^3 and exposures ranged from 0.11 to 11.2 mg/m^3 with a high silica content, ranging from 86 to 98%. The TWA exposure of stone crushing laborers in India for $PM_{2.5}$ c-silica was 2.29 mg/m^3 (Semple et al. 2008). Occupational exposure to silica was evaluated at slate pencil manufacturing units in India (Fulekar and Khan 1995). Total and respirable dust was present at concentrations up to 380.50 and 31.44 mg/m^3, respectively, based on data from the study performed in 1977. Total and respirable dust was present at concentrations as low as 4.04 and 0.61 mg/m^3, respectively, in a study performed in 1991. The free silica content was 35–40, 42–47, and 35–47% in three studies performed in 1977, 1982, and 1991 respectively.

Quartz exposure levels were measured in the Alta, Northern Norway slate industry (Bang and Suhr 1998). The slate factory had respirable quartz average concentrations of 0.12 mg/m^3 inside and 0.13 mg/m^3 outside. c-Silica exposure was measured in the Norwegian silicon carbide industry using 720 fiber samples, 720 respirable dust samples, and 1,400 total dust samples (Foreland et al. 2008). Respirable cristobalite geometric mean levels ranged from below the limit of detection to 0.038 mg/m^3 (geometric standard deviation of 2.0). Respirable quartz geometric mean levels ranged from below the limit of detection to 0.020 mg/m^3 (geometric standard deviation of 2.1). Personal airborne geometric mean concentrations of quartz and cristobalite were 0.013 mg/m^3 (geometric standard deviation of 4.58) and 0.010 mg/m^3 (geometric standard deviation of 2.10) for workers performing the carboselector job (Dion et al. 2005). The workers with the job title, Attendant in Acheson furnace maintenance, had a geometric mean quartz exposure of 0.079 mg/m^3 (geometric standard deviation of 1.49).

During the hydraulic fracturing process, large quantities of silica sand, with up to 99% silica, are used for pumping into wells at high pressure (Chalupka 2012). Data from 111 personal breathing zone samples at 11 sites in five states were evaluated by NIOSH to determine worker exposures to respirable c-silica during hydraulic fracturing (Esswein et al. 2013). The median percentage of quartz in 111 personal breathing zone samples was 53%. Total geometric mean concentrations of respirable quartz were 0.122 mg/m^3 for all samples and the geometric standard deviation was 1.152. Workers with the job titles, T-belt Operator and Sand Mover Operator, had the highest geometric mean concentrations of respirable c-silica of 0.327 and 0.259 mg/m^3, respectively, compared to other job titles.

Operations in the ceramic, brick, and clay industries result in c-silica emissions through kiln drying of clay and brick objects, crystalline sand processing, glass manufacturing, calcining of diatomaceous earth, and pottery manufacturing (EPA 1996). Birk et al. (2010) evaluated respirable c-silica measurements obtained from 1955 to 2006 for worker exposure in the ceramics industry. Typically, the highest exposure occurred in the historic samples obtained in 1955–1959 for all job task activities. The highest exposure geometric mean concentration of respirable c-silica in the 2000–2006 data set was from the preparation task at 0.03 mg/m^3. A heavy clay industry exposure study was performed with 18 factories from England and Scotland and 1,400 personal dust samples (Love et al. 1999). Mean quartz concentrations ranged from 0.04 to 0.62 mg/m^3 for non-process workers and kiln demolition workers, respectively. Respirable α-quartz concentrations were measured for workers in the refractory material manufacturing industries (Chen et al. 2007). A minimum variance unbiased estimate of the arithmetic mean respirable α-quartz content ranged from 0.0298 mg/m^3 in the crushing area to 0.0681 mg/m^3 in the mixing area.

OSHA sampling on the melt deck and sprue line of a ductile and malleable iron foundry detected c-silica at 0.21 mg/m^3 based on the TWA; however, employees engaged in the furnace cleaning and scrapping were exposed to 7.92 and 0.54 mg/m^3, respectively (Strelec 2010). Personal monitors were used to collect 158 measurements of respirable quartz from jobs conducted from 1993 to 1998 (Maxim et al. 1999). Most of the respirable c-silica concentrations, 91.14%, were less than the limit of detection; the remainder ranged from 0.010 to 0.100 mg/m^3. Occupational silica exposures were evaluated for workers at a grey and ductile iron foundry that manufactures heavy industrial castings, such as transmission housings for large trucks (Lee 2009). The 8-hour TWA c-silica concentrations ranged from 0.988 mg/m^3 for a molder to 4.38 mg/m^3 for a grinder based on the results obtained from personal sampling devices.

Andersson et al. (2012) performed an exposure assessment of quartz in Swedish iron foundries using both historical and current data. The job title with the highest mean quartz exposure was the furnace and ladle repair, with a total concentration of 0.42 mg/m^3, and the lowest was the core maker, with a total concentration of 0.024 mg/m^3. The arithmetic mean minimum variance unbiased estimate of respirable quartz exposure profiles for workers during a municipal waste incinerator relining ranged from 0.040 to 0.578 mg/m^3 (Shih et al. 2008). In Khaf, Iran, occupational exposure to respirable quartz was evaluated for workers at an iron ore mine (Naghizadeh et al. 2011). The maximum mean concentration of total quartz was at the crusher machine station at 26 mg/m^3 with a standard deviation of 7, and the minimum concentration was 0.012 mg/m^3 with a standard deviation of 0.002.

At a flat outdoor firing range in 2004, quartz levels were found to exceed 0.030 mg/m^3 (Mancuso et al. 2008); the likely source of the quartz was the sand on the floor of the range. In 2006, after the sand was changed, barrier curtains were added, and lava rock was added to the floor for silica exposure control, the quartz levels were below 0.018 mg/m^3. At a tunnel type outdoor firing range, personal sampling devices found quartz silica levels ranging from 0.15 to 0.21 mg/m^3. After Hurricane Sandy in 2012, clean-up workers were monitored for silica exposure (Freund et al. 2014). One measurement of 0.015 mg/m^3 taken at Rockaway, New York in the vicinity of sand was above the detection limit.

Diatomaceous earth mining, processing, and production reported respirable dust levels ranging from 0.1 to 28.2 mg/m^3 with a c-silica content ranging from <1 to 75% (IARC 1997). Diatomaceous earth workers have the potential for inhalation exposure to high levels of respirable cristobalite and quartz that may be present as impurities or from heating silica (IARC 1997; Rabovsky 1995). In industries where silica products are heated, such as refractory brick and diatomaceous earth plants and ceramic and pottery manufacturing plants, occupational exposure to cristobalite may occur (IARC 1997).

At a diatomaceous earth mining and milling facility in California, respirable c-silica average cumulative exposure was 0.29 mg/m^3 per years of employment. The c-silica content of the diatomaceous earth dusts varied from 1 to 25% from 1942 to 1994 (Park et al. 2002). Final cumulative exposures to total respirable dust and respirable c-silica dust were 7.31 mg/m^3·years (average; 168.84 maximum) and 2.16 mg/m^3·years (average; 62.52 maximum), respectively (Checkoway et al. 1997).

Occupational Exposure to Amorphous Silica. Occupational exposure to a-silica may occur in the use or manufacture of a-silica and a-silica-containing products, such as synthetic resins, plastics, lacquers, vinyl coatings, varnishes, pharmaceuticals, cosmetics, adhesives, paints, and foods (IARC 1997). Workers in other industries, such as glass, ceramics, cement, refractory brick, paper, paint, and rubber, may be exposed to various forms of a-silica when used as fillers, filters, or other purposes (NIOSH 2002). In an occupational exposure study, 1,375 inhalable synthetic a-silica dust concentration measurements were performed from five German synthetic a-silica plants producing pyrogenic and precipitated forms of silica (Morfeld et al. 2014). Mean aerodynamic diameters of the a-silica were 200 µm. Exposures were grouped into categories of low (<1 mg/m^3), medium (1–4 mg/m^3), high (4–10 mg/m^3), and peak (>10 mg/m^3). Using two different exposure estimate procedures, cumulative exposure estimates averaged 56.9 mg/m^3-years (expert assessment) and 31.8 mg/m^3-years (multiple exposure assessment). Older

studies in plants that use or produce synthetic a-silica have also reported dust concentrations ranging from 0 to 10 mg/m^3 (IARC 1997).

Diatomaceous earth miners can be exposed to natural a-silica dust during extraction, with measured respirable dust concentrations ranging from 0.1 to 28.2 mg/m^3; however, most studies are more focused on potential c-silica exposure, which ranges from <1 to 75% of respirable dust, depending upon how the diatomaceous earth is processed (IARC 1997).

Sugarcane farmers may be exposed to biogenic a-silica fibers, particularly during harvesting, cutting, and milling at concentrations ranging from 6,200 to 300,000 fibers/m^3 (IARC 1997). It should be noted that sugarcane workers are also expected to be exposed to c-silica during the harvesting process when sugarcane plants are burned (Le Blond et al. 2010). Low levels of biogenic a-silica fibers have also been reported during field preparation, harvesting, and transport of rice crops, at concentrations ranging from 0.13 to 1 fiber/mL (IARC 1997).

a-Silica fume is a byproduct of the ferrosilicon industrial process (IARC 1997). Total dust containing synthetic-precipitated a-silica was measured at three chemical plants at concentrations of 0–10.5 mg/m^3. Total dust and respirable dust from personal samples obtained from synthetic pyrogenic fumed manufacturing plants was found at median concentrations of 0.61–6.5 and 0.2–2.1 mg/m^3, respectively. One ferrosilicon industry exposure study reported 22.3% silica content (amorphous and crystalline) in total dust found at concentrations of 7.3 mg/m^3. In another ferrosilicon industry exposure study, maintenance workers had respirable dust containing a-silica exposures ranging from 0.27 to 2.24 mg/m^3.

Exposures in Children. Exposure of children to c- and a-silica from breathing air, drinking water, and eating food is expected. As both c- and a-silica are part of the natural environment and found widely in soils, rocks, water, and foods, exposure to silica is unavoidable. Children are likely to ingest dirt from their unwashed hands or when playing with soils, and may be exposed to silica in this manner. Children living in proximity to mines, quarry sites, or industries that release silica particulates to the environment may be exposed to higher levels of silica than are found in the natural environment via inhalation of silica from dust that is entrained in air. Silica is a major component of sand and dirt and may be in many forms; some of these forms may be embedded in minerals.

Dermal and oral exposure may occur through the use of consumer and commercial products that contain silica, including cleansers, skin care products and soaps, art clays and glazes, talcum powder, and

pharmaceuticals (NTP 2009). Both silicon dioxide and diatomaceous earth may be found in food and are listed on the Everything Added to Food in the United States (EAFUS) report of items added directly to food that the FDA has either approved as food additives or listed or affirmed as Generally Recognized As Safe (GRAS) (FDA 2013). However, average daily intakes and exposure information for children were not available.

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,

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/m^3, 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/m^3 (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/m^3, but not 10 mg/m^3; exposure to precipitated a-silica induced these effects after a 3-day exposure to 10 mg/m^3 (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/m^3 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/m^3 for precipitated a-silica (Reuzel et al. 1991). For colloidal silica, NOAEL and LOAEL values of 10 and 50 mg/m^3, 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/m^3 (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/m^3 (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; Mannetje 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/m^3-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/m^3-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

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/m^3, 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/m^3 and cardiac hypertrophy in monkeys at 15 mg/m^3 (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/m^3 (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

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/m^3 (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/m^3 (Groth et al. 1981; Schepers 1962). Similarly, no immune system effects were observed in rats exposed to

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/m^3 (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/m^3 (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

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

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 been 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; Dobreva 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.

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.

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). a-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. a-Silica has been found to accumulate in rice, millet, sugarcane, and wheat plants (Rabovsky 1995). No additional information is needed at this time.

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. c-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 μm 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.

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 Affair 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 Pittsburg at Pittsburg, Pittsburg, 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

Table 6-1. Ongoing Studies on Silica Compounds

Principal investigator	Study topic	Institution	Sponsor
Laskin, DL	Mechanism examining the role of caveolin-1 and TNFα 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 Pittsburg 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 Pittsburg 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.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding silica in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for silica.

Table 7-1. Regulations and Guidelines Applicable to Silica

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2018
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	No data	IRIS 2018
	Tolerance exemptions for minimal risk active and inert ingredients in pesticides		EPA 2018b
	Silica, amorphous, fumed (crystalline free)	Yes	
	Silica gel	Yes	
	Silica, vitreous	Yes	
WHO	Drinking water quality guidelines	Not listed	WHO 2017
FDA	Substances added to food[a]		
	Silicon dioxide	Approved under food additive, GRAS, and color additive regulations	FDA 2018a
	Diatomaceous earth	Approved under food additive and GRAS regulations	FDA 2018b

Table 7-1. Regulations and Guidelines Applicable to Silica

Agency	Description	Information	Reference
USDA	Nonagricultural (nonorganic) substances allowed as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))"		USDA 2018
	Silicon dioxide	Permitted as a defoamer. Allowed for other uses when organic rice hulls are not commercially available	
	Diatomaceous earth	Food filtering aid only	
	Cancer		
HHS	Carcinogenicity classification		NTP 2016
	Silica, crystalline (respirable size)	Known to be a human carcinogen	
EPA	Carcinogenicity classification	No data	IRIS 2018
IARC	Carcinogenicity classification		
	Silica, amorphous	Group 3[b]	IARC 1997
	Silica dust, crystalline, in the form of quartz or cristobalite	Group 1[c]	IARC 2012
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, construction or shipyard employment		
	Respirable crystalline silica (quartz, cristobalite, and/or tridymite)[d]	0.05 mg/m^3	OSHA 2018a, OSHA 2018b, OSHA 2018c, OSHA 2018d
	Amorphous silica, including natural diatomaceous earth	80 mg/m^3/%SiO2	OSHA 2018c
	PEL (8-hour TWA) for any operations or sectors where the exposure limit in 29 CFR 1910.1053 is stayed or is otherwise not in effect		OSHA 2018c
	Quartz (respirable)	10 mg/m^3/(%SiO2+2)	
	Cristoballite, tridymite	Use 1⁄2 the value calculated from the formula for quartz	
NIOSH	REL (up to 10-hour TWA)		
	Silica, amorphous	6 mg/m^3	NIOSH 2016a
	Silica, crystalline (as respirable dust)	0.05 mg/m^3 [e]	NIOSH 2016b
	IDLH		
	Silica, amorphous	3,000 mg/m^3	NIOSH 1994a
	Silica, crystalline (as respirable dust; cristobalite, tridymite)	25 mg/m^3	NIOSH 1994b
	Silica, crystalline (as respirable dust; quartz, tripoli)	50 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Silica

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2016
DOE	PACs-air		DOE 2018b
	PAC-1[f]		
	Silica amorphous hydrated	18 mg/m^3	
	Silica, crystalline-quartz (silicon dioxide)	0.075 mg/m^3	
	Cristobalite	0.075 mg/m^3	
	Silica, amorphous fumed	18 mg/m^3	
	Silica gel, amorphous synthetic	18 mg/m^3	
	Silica gel	18 mg/m^3	
	PAC-2[f]		
	Silica amorphous hydrated	740 mg/m^3	
	Silica, crystalline-quartz (silicon dioxide)	33 mg/m^3	
	Cristobalite	33 mg/m^3	
	Silica, amorphous fumed	100 mg/m^3	
	Silica gel, amorphous synthetic	200 mg/m^3	
	Silica gel	200 mg/m^3	
	PAC-3[f]		
	Silica amorphous hydrated	4,500 mg/m^3	
	Silica, crystalline-quartz (silicon dioxide)	200 mg/m^3	
	Cristobalite	200 mg/m^3	
	Silica, amorphous fumed	630 mg/m^3	
	Silica gel, amorphous synthetic	1,200 mg/m^3	
	Silica gel	1,200 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group 3: Not classifiable as to its carcinogenicity to humans.
[c]Group 1: Carcinogenic to humans.
[d]In addition to limiting exposures, employers must take other steps to protect workers. The construction standard includes specific exposure control methods.
[e]Potential occupational carcinogen.
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018a).

AEGL = acute exposure guideline level; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; mppcf = millions of particles per cubic foot; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; USDA = U.S. Department of Agriculture; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for c-silica.

Rationale for Not Deriving an MRL: No adverse effects or critical targets have been associated with acute-duration exposure to inhaled c-silica. Therefore, an acute-duration inhalation MRL for c-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for c-silica.

Rationale for Not Deriving an MRL: Silicosis has been observed in workers exposed to "intense exposure" of fine c-silica dusts, such as those generated during sandblasting and denim sand blasting, for intermediate durations. However, no estimates of quantitative exposure data has been defined for "intense exposure." Furthermore, silicosis is a serious adverse effect that has the potential to cause death due to respiratory failure or lung cancer. Consistent with ATSDR's practice, LOAELs for serious health effects are not used as a basis for establishing MRLs. Therefore, an intermediate-duration inhalation MRL for c-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for c-silica.

Rationale for Not Deriving an MRL: Silicosis is the most sensitive effect of chronic-duration inhalation exposure to c-silica (see results of numerous studies summarized in Section 2.4). However, no NOAEL or threshold level for silicosis have been identified. In occupational studies, silicosis was observed for the lowest reported cumulative exposure range of 0–0.2 mg/m^3-year (Steenland and Brown 1995a). Although several studies have identified LOAEL values for silicosis, silicosis is a serious adverse effect that has the potential to cause death due to respiratory failure or lung cancer. Consistent with ATSDR's practice, LOAELs for serious health effects are not used as a basis for establishing MRLs. Given the serious nature of silicosis, a chronic-duration inhalation MRL for c-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for c-silica.

Rationale for Not Deriving an MRL: Few studies on acute oral exposure to c-silica were identified and the available studies in laboratory animals do not identify critical effects (Oner et al. 2005, 2006). Given the ubiquitous nature of c-silica in the environment, it is assumed that incidental oral exposure of humans commonly occurs. No reports of adverse effects associated with incidental oral exposure to c-silica in the environment were identified. An acute-duration oral MRL for c-silica was not derived due to the lack of data identifying sensitive targets of the toxicity and the lack of dose-response data.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for c-silica.

Rationale for Not Deriving an MRL: Only one intermediate-duration oral exposure study on c-silica was identified (Dobbie and Smith 1982), and this study did not identify any critical effects associated with intermediate oral exposure. Given the ubiquitous nature of c-silica in the environment, it is assumed that incidental oral exposure of humans commonly occurs. No reports of adverse effects associated with incidental oral exposure to c-silica in the environment were identified. Therefore, an intermediate-duration oral MRL for c-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Crystalline silica (c-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for c-silica.

Rationale for Not Deriving an MRL: Two epidemiological studies evaluating effects of oral silica in drinking water on cognitive function did not find decreased cognitive function (Gillette-Guyonnet et al. 2005; Jacqmin-Gadda et al. 1996). However, these studies did not report the identity of the silica compound in water (e.g., c-silica or a-silica). No chronic-duration oral exposure studies on c-silica in animals were identified. Given the ubiquitous nature of c-silica in the environment, it is assumed that incidental oral exposure of humans commonly occurs. No reports of adverse effects associated with incidental oral exposure to c-silica in the environment were identified. The lack of toxicity data precludes derivation of a chronic-duration oral MRL for c-silica.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for a-silica.

Rationale for Not Deriving an MRL: Results of the animal studies provide evidence that toxicological potency for respiratory effects can differ between different a-silica polymorphs (Arts et al. 2007; ECHA 2019; Johnson et al. 2000; Lee and Reuzel et al. 1991; Reuzel et al. 1991; Schepers et al. 1957b; Warheit et al. 1991, 1995). For example, serious respiratory distress and inflammation were observed in rats exposed to 17 mg/m^3 of fumed hydrophilic silica (Aerosil 200) for 6 hours/day, 5 days/week for 2 weeks (Reuzel et al. 1991), whereas under the same exposure conditions, the only adverse respiratory effect observed for colloidal silica (Ludox) was an increase in neutrophils in bronchoalveolar lavage fluid at 50.5 mg/m^3 (Warheit et al. 1991, 1995). 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, an acute-duration inhalation MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for a-silica.

Rationale for Not Deriving an MRL: Results of the animal studies provide evidence that toxicological potency for respiratory effects can differ between different a-silica polymorphs (ECHA 20019; Johnson et al. 2000; Lee and Kelly 1992; Reuzel et al. 1991; Rosenbrunch 1992; Warheit et al. 1991, 1995; Schepers et al. 1957a,b,c; Tebbens et al. 1957; Warheit et al. 1991, 1995). For example, serious respiratory inflammation and fibrosis were observed in rats exposed to 1 mg/m^3 of pyrogenic hydrophilic silica (Aerosil 200) for 6 hours/day, 5 days/week for 13 weeks (Reuzel et al. 1991), whereas under the same exposure conditions, the only adverse respiratory effect observed for colloidal silica (Ludox) was an increase in neutrophils in bronchoalveolar lavage fluid at 50.5 mg/m^3 (Warheit et al. 1991, 1995). 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, an intermediate-duration inhalation MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for a-silica.

Rationale for Not Deriving an MRL: As discussed above for the acute- and chronic-duration inhalation MRLs for a-silica, results of the animal studies provide evidence that toxicological potency for respiratory effects can differ between different a-silica polymorphs. However, available chronic-duration inhalation studies in animals do not provide sufficient information to determine if the toxicological potency for respiratory effects can differ between different a-silica polymorphs. Studies have reported NOAEL values for respiratory effects of 6.9–15 mg/m^3 (Groth et al. 1981; Schepers 1962); however, these studies did not examine effects of higher exposures. In a series of studies conducted by Schepers (1981), adverse respiratory effects were observed at 126 mg/m^3; however, lower exposures were not evaluated. 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, a chronic-duration inhalation MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for a-silica.

Rationale for Not Deriving an MRL: Published and unpublished studies have evaluated the effects of acute-duration oral exposure of animals to a-silica (ECHA 2016; Lewison et al. 1994). These studies, which examined numerous toxicological endpoints, have not identified critical effects associated with acute-duration oral exposure. Therefore, an acute-duration oral MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for a-silica.

Rationale for Not Deriving an MRL: Published and unpublished studies have evaluated the effects of intermediate-duration oral exposure of animals to a-silica (ECHA 2019; Lewison et al. 1994; Newberne and Wilson 2970; Takizawa et al. 1988; Woterbeek et al. 2015). These studies, which examined numerous toxicological endpoints, have not identified critical effects associated intermediate-duration oral exposure. Therefore, an intermediate-duration oral MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Amorphous silica (a-silica)
CAS Numbers: Various
Date: September 2019
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for a-silica.

Rationale for Not Deriving an MRL: Few published and unpublished animal studies have evaluated the effects of chronic-duration oral exposure of animals to a-silica (ECHA 2019; Takizawa et al. 1988). These studies, which examined numerous toxicological endpoints, have not identified critical effects associated chronic-duration oral exposure. Therefore, a chronic-duration oral MRL for a-silica was not derived.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR SILICA

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to silica.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for silica. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of silica have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of silica are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for silica released for public comment in 2017. The following main databases were searched in January 2018:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for silica. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases

were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to silica were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
01/2018	((2014/02/01:3000[dp] OR 2015/02/01:3000[mhda]) AND ((("silicon dioxide"[mh] AND silicosis[mh]) AND (amorphous[tw] OR calcined[tw])) OR (("silicon dioxide"[mh:noexp]) AND (("Silicon Dioxide/toxicity"[MeSH Terms] OR "Silicon Dioxide/adverse effects"[MeSH Terms] OR "Silicon Dioxide/poisoning"[MeSH Terms] OR "Silicon Dioxide/pharmacokinetics"[MeSH Terms] OR "Silicon Dioxide/blood"[MeSH Terms] OR "Silicon Dioxide/cerebrospinal fluid"[MeSH Terms] OR "Silicon Dioxide/urine"[MeSH Terms] OR "Silicon Dioxide/antagonists and inhibitors"[MeSH Terms]) OR ("Silicon Dioxide"[MeSH Terms] AND ("chemically induced"[MeSH Subheading] OR "environmental exposure"[MeSH Terms] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Silicon Dioxide"[MeSH Terms] AND ("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR ("Silicon Dioxide/metabolism"[MeSH Terms] AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR ("Silicon Dioxide/pharmacology"[Majr]))) OR ("Quartz/toxicity"[MeSH Terms] OR "Quartz/adverse effects"[MeSH Terms] OR "Quartz/poisoning"[MeSH Terms] OR "Quartz/pharmacokinetics"[MeSH Terms] OR "Quartz/blood"[MeSH Terms] OR "Quartz/cerebrospinal fluid"[MeSH Terms] OR "Quartz/urine"[MeSH Terms] OR "Quartz/antagonists and inhibitors"[MeSH Terms]) OR ("Quartz"[MeSH Terms] AND ("chemically induced"[MeSH Subheading] OR "environmental exposure"[MeSH Terms] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Quartz"[MeSH Terms] AND ("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase

Table B-2. Database Query Strings

Database search date	Query string
	Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR ("Quartz/metabolism"[MeSH Terms] AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR ("Quartz/pharmacology"[Majr]) OR ("Diatomaceous earth/toxicity"[MeSH Terms] OR "Diatomaceous earth/adverse effects"[MeSH Terms] OR "Diatomaceous earth/poisoning"[MeSH Terms] OR "Diatomaceous earth/pharmacokinetics"[MeSH Terms] OR "Diatomaceous earth/blood"[MeSH Terms] OR "Diatomaceous earth/cerebrospinal fluid"[MeSH Terms] OR "Diatomaceous earth/urine"[MeSH Terms] OR "Diatomaceous earth/antagonists and inhibitors"[MeSH Terms]) OR ("Diatomaceous earth"[MeSH Terms] AND ("chemically induced"[MeSH Subheading] OR "environmental exposure"[MeSH Terms] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Diatomaceous earth"[MeSH Terms] AND ("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR ("Diatomaceous earth/metabolism"[MeSH Terms] AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR ("Diatomaceous earth/pharmacology"[Majr]) OR ("Silica Gel/toxicity"[MeSH Terms] OR "Silica Gel/adverse effects"[MeSH Terms] OR "Silica Gel/poisoning"[MeSH Terms] OR "Silica Gel/pharmacokinetics"[MeSH Terms] OR "Silica Gel/blood"[MeSH Terms] OR "Silica Gel/cerebrospinal fluid"[MeSH Terms] OR "Silica Gel/urine"[MeSH Terms] OR "Silica Gel/antagonists and inhibitors"[MeSH Terms]) OR ("Silica Gel"[MeSH Terms] AND ("chemically induced"[MeSH Subheading] OR "environmental exposure"[MeSH Terms] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Silica Gel"[MeSH Terms] AND ("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR ("Silica Gel/metabolism"[MeSH Terms] AND ("humans"[MeSH Terms] OR "animals"[MeSH Terms])) OR ("Silica Gel/pharmacology"[Majr]) OR ("Beta-Quartz glass-ceramic"[nm]) OR (("17679-64-0"[tw] OR "Keatite"[tw] OR "13778-38-6"[tw] OR "Coesite"[tw] OR "13778-37-5"[tw] OR "Stishovite"[tw] OR "92283-58-4"[tw] OR "Moganite"[tw] OR "Dioxosilane"[tw] OR "Dioxo-silane"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and

Table B-2. Database Query Strings

Database search date	Query string
	hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh])) OR "pharmacology"[Majr] OR silicon dioxide/ai)) OR ("Silicosis/analysis"[Mesh] OR "Silicosis/anatomy and histology"[Mesh] OR "Silicosis/blood"[Mesh] OR "Silicosis/chemically induced"[Mesh] OR "Silicosis/classification"[Mesh] OR "Silicosis/complications"[Mesh] OR "Silicosis/cytology"[Mesh] OR "Silicosis/diagnosis"[Mesh] OR "Silicosis/enzymology"[Mesh] OR "Silicosis/epidemiology"[Mesh] OR "Silicosis/ethnology"[Mesh] OR "Silicosis/etiology"[Mesh] OR "Silicosis/genetics"[Mesh] OR "Silicosis/history"[Mesh] OR "Silicosis/immunology"[Mesh] OR "Silicosis/metabolism"[Mesh] OR "Silicosis/microbiology"[Mesh] OR "Silicosis/mortality"[Mesh] OR "Silicosis/pathology"[Mesh] OR "Silicosis/physiology"[Mesh] OR "Silicosis/physiopathology"[Mesh] OR "Silicosis/prevention and control"[Mesh] OR "Silicosis/psychology"[Mesh] OR "Silicosis/radiography"[Mesh] OR "Silicosis/radionuclide imaging"[Mesh] OR "Silicosis/statistics and numerical data"[Mesh] OR "Silicosis/ultrasonography"[Mesh] OR "Silicosis/urine"[Mesh] OR "Silicosis/veterinary"[Mesh] OR "Silicosis/virology"[Mesh]) OR ("silicosis"[mh] NOT silicosis/*[mh]))) OR ((2014/02/01:3000[dp] OR 2015/02/01:3000[crdat] OR 2015/02/01:3000[edat]) AND ("Accusand"[ti] OR "Aerosil"[ti] OR "Agate"[ti] OR "alpha-Cristobalite"[ti] OR "alpha-Crystobalite"[ti] OR "alpha-Quartz"[ti] OR "alpha-Tridymite"[ti] OR "Amethyst"[ti] OR "beta-Quartz"[ti] OR "Cab-O-sil"[ti] OR "Celatom"[ti] OR "Celite"[ti] OR "Chalcedony"[ti] OR "Cherts"[ti] OR "Chromaton"[ti] OR "Chromosorb G"[ti] OR "Chromosorb P"[ti] OR "Coesite"[ti] OR "Corasil II"[ti] OR "Cristobalit"[ti] OR "Cristobalite"[ti] OR "Cristoballite"[ti] OR "Crystobalite"[ti] OR "Crystoballite"[ti] OR "cuarzo"[ti] OR "Diatomaceous earth"[ti] OR "Diatomite"[ti] OR "Dicalite"[ti] OR "Dioxosilane"[ti] OR "DQ12"[ti] OR "Dri-Die"[ti] OR "Extrelut"[ti] OR "FIBROUS GLASS"[ti] OR "Flint"[ti] OR "Infusorial earth"[ti] OR "Kieselguhr"[ti] OR "Ludox"[ti] OR "Micro-cel"[ti] OR "Min-U-Sil"[ti] OR "Moganite"[ti] OR "Nalcoag"[ti] OR "Neosyl"[ti] OR "Novaculite"[ti] OR "Nyacol"[ti] OR "Porasil"[ti] OR "Quartz"[ti] OR "Quartz-beta"[ti] OR "Quarz"[ti] OR "Siderite"[ti] OR "Sikron F 600"[ti] OR "Silica"[ti] OR "Siliceous earth"[ti] OR "Silicic anhydride"[ti] OR "Silicon dioxide"[ti] OR "Silicon oxide"[ti] OR "Silicone dioxide"[ti] OR "Siloxid"[ti] OR "Siltex"[ti] OR "sio2"[ti] OR "Sipernat"[ti] OR "Snowit"[ti] OR "Spectrosil"[ti] OR "Suprasil"[ti] OR "Tridimite"[ti] OR "Tridymit"[ti] OR "Tridymite"[ti] OR ("Tripoli"[ti] NOT ("libya"[tw] OR "lebanon"[tw])) OR "Zipax"[ti] OR "Zorbax sil"[ti] OR "a-Cristobalite"[ti] OR "a-Crystobalite"[ti] OR "a-Quartz"[ti]) NOT medline[sb]))
	"Acticel"[tw] OR "Admafine SO 25H"[tw] OR "Admafine SO 25R"[tw] OR "Admafine SO 32H"[tw] OR "Admafine SO-C 2"[tw] OR "Admafine SO-C 3"[tw] OR "Aerogel 200"[tw] OR "AF-SO 25R"[tw] OR "Aquafil"[tw] OR "Armsorb GKhI"[tw] OR "As 1 (silica)"[tw] OR "Belcron B 6000"[tw] OR "BF 100"[tw] OR "Borsil P"[tw] OR "Cab-O-grip II"[tw] OR "Cab-O-sperse"[tw] OR "Cabosil N 5"[tw] OR "Cabosil st-1"[tw] OR "Calofrig FJ"[tw] OR "Carplex"[tw] OR "Cataloid"[tw] OR "Christensenite"[tw] OR "Chromatron N Super"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Corning 7940"[tw] OR "CP-SilicaPLOT"[tw] OR "cristobalita"[tw] OR "CRS 1101-17"[tw] OR "CRS 1102RD8"[tw] OR "Crystalite 5K"[tw] OR "Crystalite A 1"[tw] OR "Crystalite A 2"[tw] OR "Crystalite AA"[tw] OR "Crystalite C"[tw] OR "Crystalite CRS"[tw] OR "Crystalite SS"[tw] OR "Crystalite VX-S"[tw] OR "Crystalite VX-SR"[tw] OR "Crystalite VX-X"[tw] OR "Crysvarl"[tw] OR "Denka F 90"[tw] OR "Denka FB 30"[tw] OR "Denka FB 44"[tw] OR "Denka FB 74"[tw] OR "Denka FS 30"[tw] OR "Elsil 100"[tw] OR "Elsil BF 100"[tw] OR "ENT 25,550"[tw] OR "EQ 912"[tw] OR "Extrusil"[tw] OR "Flintshot"[tw] OR "Fossil flour"[tw] OR "Fuselex"[tw] OR "Gold bond R"[tw] OR "GP 11I"[tw] OR "GP 7I"[tw] OR "HK 400"[tw] OR "Inducarb 0.5-1"[tw] OR "Keatite (SiO2)"[tw] OR "Manosil vn 3"[tw] OR "Marshalite"[tw] OR "Metacristobalite"[tw] OR "Mikrosil LM 300"[tw] OR "Mikrosil SP 10"[tw] OR "Mikrosil SP 3"[tw] OR "Millisil W 12"[tw] OR "Millisil W 3"[tw] OR "Millisil W 6"[tw] OR "Millisil W 6EST"[tw] OR "N1030"[tw] OR "Nalcast"[tw] OR "Nalco 1050"[tw] OR "Nalfloc N 1050"[tw] OR "Neosil"[tw] OR "Optocil"[tw] OR "Pigment White 27"[tw] OR "Plastorit"[tw] OR "Positive sol 130M"[tw] OR "Positive sol 232"[tw] OR "QG 100"[tw] OR "Quso 51"[tw] OR "Quso G 30"[tw] OR "Rancosil"[tw] OR "Randanite"[tw] OR "Rock crystal"[tw] OR "Santocel"[tw] OR "Sg-67"[tw] OR "Sibelco B 0012"[tw] OR "Sibelco M 10"[tw] OR "Sibelite M 3000"[tw] OR "Sibelite M 4000"[tw] OR "Sibelite M 6000"[tw] OR "Sicron F 300"[tw] OR "Sifraco C 10"[tw] OR "Sifraco C 600"[tw] OR "Sihelco B 2500"[tw] OR "Sikron 3000"[tw] OR "Sikron F 100"[tw] OR "Sikron H 200"[tw] OR "Sikron H 500"[tw] OR "Sikron H 600"[tw] OR "Sikron SF 300"[tw] OR "Sikron SF 500"[tw] OR "Sikron SF 600"[tw] OR "Sikron SF 6000"[tw] OR "Sikron SF 800"[tw] OR "Sil-Co-Sil"[tw] OR "Silane, dioxo-"[tw] OR "Silanox 101"[tw] OR "Silbond 006MST"[tw] OR "Silbond 3000MST"[tw] OR "Silbond 600EST"[tw] OR "Silbond FW 600EST"[tw] OR "Silbond FW 61EST"[tw] OR "Silbond VP 810-10/1EST"[tw] OR "Silcron F 600"[tw] OR "Silikil"[tw] OR "Silikill"[tw] OR "Sillikolloid"[tw] OR "Silver bond B"[tw] OR "Silverbond 200"[tw] OR "Silverbond 325"[tw] OR "Snowtex 30"[tw] OR "Snowtex O"[tw] OR "Stishovite (SiO2)"[tw] OR "Syton 2X"[tw] OR "TGL 16319"[tw] OR "Tokusil TPLM"[tw] OR "tridimita"[tw] OR "Ultrasil VH 3"[tw] OR "Ultrasil VN 3"[tw] OR "Vitasil 220"[tw] OR "Vitreosil IR"[tw] OR "Vulkasil"[tw] OR "W 006"[tw] OR "Wessalon"[tw] OR "WGL 300"[tw] OR "Zeofree 80"[tw]
Toxline	
01/2018	(7631-86-9 [rn] OR 14808-60-7 [rn] OR 61790-53-2 [rn] OR 68855-54-9 [rn] OR 99439-28-8 [rn] OR 14464-46-1 [rn] OR 1317-95-9 [rn] OR 15468-32-3 [rn] OR 112945-52-5 [rn] OR 112926-00-8 [rn] OR 60676-86-0 [rn] OR 17679-64-0 [rn] OR 13778-38-6 [rn] OR 13778-37-5 [rn] OR 92283-58-4 [rn]) AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("accusand" OR "aerosil" OR "agate" OR "alpha cristobalite" OR "alpha crystobalite" OR "alpha quartz" OR "alpha tridymite" OR "beta quartz" OR "cab o sil" OR "celatom" OR "celite" OR "chalcedony" OR "cherts" OR "chromaton" OR "chromosorb g" OR "chromosorb p" OR "coesite" OR "corasil ii" OR "cristobalit" OR "cristobalite" OR "cristoballite" OR "crystobalite" OR "crystoballite" OR "cuarzo" OR "diatomaceous earth" OR "diatomaceous silica" OR "diatomite" OR "dicalite" OR "dioxosilane" OR "dq12" OR "dri die" OR "extrelut" OR "fibrous glass" OR "flint" OR "infusorial earth" OR "kieselguhr") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings

Database search date	Query string
	("acticel" OR "admafine so 25h" OR "admafine so 25r" OR "admafine so 32h" OR "admafine so c 2" OR "admafine so c 3" OR "aerogel 200" OR "af so 25r" OR "aquafil" OR "armsorb gkhi" OR "as 1 (silica) " OR "belcron b 6000" OR "bf 100" OR "borsil p" OR "cab o grip ii" OR "cab o sperse" OR "cabosil n 5" OR "cabosil st 1" OR "calofrig fj" OR "carplex" OR "cataloid" OR "christensenite" OR "chromatron n super" OR "corning 7940" OR "cp silicaplot" OR "cristobalita" OR "crs 1101 17" OR "crs 1102rd8" OR "crystalite 5k" OR "crystalite a 1" OR "crystalite a 2" OR "crystalite aa" OR "crystalite c" OR "crystalite crs" OR "crystalite ss" OR "crystalite vx s" OR "crystalite vx sr" OR "crystalite vx x" OR "crysvarl") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org])
	("denka f 90" OR "denka fb 30" OR "denka fb 44" OR "denka fb 74" OR "denka fs 30" OR "elsil 100" OR "elsil bf 100" OR "ent 25 550" OR "eq 912" OR "extrusil" OR "flintshot" OR "fossil flour" OR "fuselex" OR "gold bond r" OR "gp 11i" OR "gp 7i" OR "hk 400" OR "inducarb 0 5 1" OR "keatite (sio2) " OR "manosil vn 3" OR "marshalite" OR "metacristobalite" OR "mikrosil lm 300" OR "mikrosil sp 10" OR "mikrosil sp 3" OR "millisil w 12" OR "millisil w 3" OR "millisil w 6" OR "millisil w 6est" OR "Moganite" OR "n1030" OR "nalcast" OR "nalco 1050" OR "nalfloc n 1050" OR "neosil" OR "optocil" OR "pigment white 27" OR "plastorit" OR "positive sol 130m" OR "positive sol 232" OR "qg 100" OR "quso 51" OR "quso g 30") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("ludox" OR "micro cel" OR "min u sil" OR "nalcoag" OR "neosyl" OR "novaculite" OR "nyacol" OR "porasil" OR "quartz" OR "quartz beta" OR "quarz" OR "siderite" OR "sikron f 600" OR "silica" OR "siliceous earth" OR "silicic anhydride" OR "silicon dioxide" OR "silicon oxide" OR "silicone dioxide" OR "siloxid" OR "siltex" OR "sipernat" OR "snowit" OR "spectrosil" OR "suprasil" OR "tridimite" OR "tridymit" OR "tridymite" OR "tripoli" OR "zipax" OR "zorbax sil" OR "a cristobalite" OR "a crystobalite" OR "a quartz") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("rancosil" OR "randanite" OR "rock crystal" OR "santocel" OR "sg 67" OR "sibelco b 0012" OR "sibelco m 10" OR "sibelite m 3000" OR "sibelite m 4000" OR "sibelite m 6000" OR "sicron f 300" OR "sifraco c 10" OR "sifraco c 600" OR "sihelco b 2500" OR "sikron 3000" OR "sikron f 100" OR "sikron h 200" OR "sikron h 500" OR "sikron h 600" OR "sikron sf 300" OR "sikron sf 500" OR "sikron sf 600" OR "sikron sf 6000" OR "sikron sf 800" OR "sil co sil" OR "silane dioxo " OR "silanox 101" OR "silbond 006mst" OR "silbond 3000mst" OR "silbond 600est" OR "silbond fw 600est" OR "silbond fw 61est" OR "silbond vp 810 10 1est" OR "silcron f 600" OR "silikil" OR "silikill" OR "sillikolloid" OR "silver bond b" OR "silverbond 200" OR "silverbond 325" OR "snowtex 30" OR "snowtex o" OR "stishovite (sio2) " OR "syton 2x" OR "tgl 16319" OR "tokusil tplm" OR "tridimita" OR "ultrasil vh 3" OR "ultrasil vn 3" OR "vitasil 220" OR "vitreosil ir" OR "vulkasil" OR "w 006" OR "wessalon" OR "wgl 300" OR "zeofree 80") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings

Database search date	Query string
Toxcenter	
01/2018	=> d hist full (FILE 'HOME' ENTERED AT 12:14:48 ON 18 JAN 2018) FILE 'TOXCENTER' ENTERED AT 12:16:10 ON 18 JAN 2018 CHARGED TO COST=EH011.05.LB.02.05 L1 101729 SEA 7631-86-9 OR 14808-60-7 OR 61790-53-2 OR 68855-54-9 OR 99439-28-8 OR 14464-46-1 OR 1317-95-9 OR 15468-32-3 OR 112945-52-5 OR 112926-00-8 OR 60676-86-0 OR 17679-64-0 OR 13778-38-6 OR 13778-37-5 OR 92283-58-4 L2 11170 SEA SILICOSIS/TI,CT,ST,IT L3 110260 SEA L1 OR L2 L4 66684 SEA L3 NOT (PATENT/DT OR TSCATS/FS) L5 12750 SEA L4 AND PY>=2014 ACT TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L21 QUE (ENDOCRIN? AND DISRUPT?) L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 5004 SEA L5 AND L36
	L40 1410 SEA L39 AND MEDLINE/FS
	L41 453 SEA L39 AND BIOSIS/FS
	L42 3124 SEA L39 AND CAPLUS/FS
	L43 17 SEA L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 4295 DUP REM L40 L41 L43 L42 (709 DUPLICATES REMOVED)
	L*** DEL 1410 S L39 AND MEDLINE/FS
	L*** DEL 1410 S L39 AND MEDLINE/FS
	L45 1410 SEA L44
	L*** DEL 453 S L39 AND BIOSIS/FS
	L*** DEL 453 S L39 AND BIOSIS/FS
	L46 270 SEA L44
	L*** DEL 3124 S L39 AND CAPLUS/FS
	L*** DEL 3124 S L39 AND CAPLUS/FS
	L47 2601 SEA L44
	L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L48 14 SEA L44
	L49 2885 SEA (L45 OR L46 OR L47 OR L48) NOT MEDLINE/FS D SCAN L49

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
02/2019	Compounds searched: 7631-86-9; 14808-60-7; 99439-28-8; 14464-46-1; 1317-95-9; 15468-32-3; 112945-52-5; 112926-00-8; 61790-53-2; 60676-86-0; 68855-54-9; 17679-64-0; 13778-38-6; 13778-37-5; 92283-58-4
NTP	
01/2018	"7631-86-9" OR "14808-60-7" OR "61790-53-2" OR "68855-54-9" OR "99439-28-8" OR "14464-46-1" OR "1317-95-9" OR "15468-32-3" OR "112945-52-5" OR "112926-00-8" OR "60676-86-0" OR "17679-64-0" OR "13778-38-6" OR "13778-37-5" OR "92283-58-4"
	"Accusand" OR "Aerosil" OR "Agate" OR "alpha-Cristobalite" OR "alpha-Crystobalite" OR "alpha-Quartz" OR "alpha-Tridymite" OR "beta-Quartz" OR "Cab-O-sil" OR "Celatom" OR "Celite" OR "Chalcedony" OR "Cherts" OR "Chromaton" OR "Chromosorb G" OR "Chromosorb P" OR "Coesite" OR "Corasil II" OR "Cristobalit" OR "Cristobalite" OR "Cristoballite" OR "Crystobalite" OR "Crystoballite" OR "cuarzo" OR "Diatomaceous earth" OR "Diatomaceous silica" OR "Diatomite" OR "Dicalite" OR "Dioxosilane" OR "DQ12" OR "Dri-Die" OR "Extrelut" OR "FIBROUS GLASS" OR "Flint" OR "Infusorial earth" OR "Kieselguhr" OR "Ludox" OR "Micro-cel" OR "Min-U-Sil" OR "Moganite" OR "Nalcoag" OR "Neosyl" OR "Novaculite" OR "Nyacol" OR "Porasil" OR "Quartz" OR "Quartz-beta" OR "Quarz" OR "Siderite" OR "Sikron F 600" OR "Silica" OR "Siliceous earth" OR "Silicic anhydride" OR "Silicon dioxide" OR "Silicon oxide" OR "Silicone dioxide" OR "Siloxid" OR "Siltex" OR "Sipernat" OR "Snowit" OR "Spectrosil" OR "Suprasil" OR "Tridimite" OR "Tridymit" OR "Tridymite" OR "Tripoli" OR "Zipax" OR "Zorbax sil" OR "a-Cristobalite" OR "a-Crystobalite" OR "a-Quartz"
Regulations.gov	
02/2019	Compounds searched: 7631-86-9; 14808-60-7; 99439-28-8; 14464-46-1; 1317-95-9; 15468-32-3; 112945-52-5; 112926-00-8; 61790-53-2; 60676-86-0; 68855-54-9; 17679-64-0; 13778-38-6; 13778-37-5; 92283-58-4
NIH RePORTER	
02/2019	Active projects: "Accusand" OR "Aerosil" OR "Agate" OR "alpha-Cristobalite" OR "alpha-Crystobalite" OR "alpha-Quartz" OR "alpha-Tridymite" OR "Amethyst" OR "beta-Quartz" OR "Cab-O-sil" OR "Celatom" OR "Celite" OR "Chalcedony" OR "Cherts" OR "Chromaton" OR "Chromosorb G" OR "Chromosorb P" OR "Coesite" OR "Corasil II" OR "Cristobalit" OR "Cristobalite" OR "Cristoballite" OR "Crystobalite" OR "Crystoballite" OR "cuarzo" OR "Diatomaceous earth" OR "Diatomite" OR "Dicalite" OR "Dioxosilane" OR "DQ12" OR "Dri-Die" OR "Extrelut" OR "FIBROUS GLASS" OR "Flint" OR "Infusorial earth" OR "Kieselguhr" OR "Ludox" OR "Micro-cel" OR "Min-U-Sil" OR "Moganite" OR "Nalcoag" OR "Neosyl" OR "Novaculite" OR "Nyacol" OR "Porasil" OR "Quartz" OR "Quartz-beta" OR "Quarz" OR "Siderite" OR "Sikron F 600" OR "Silica" OR "Siliceous earth" OR "Silicic anhydride" OR "Silicon dioxide" OR "Silicon oxide" OR "Silicone dioxide" OR "Siloxid" OR "Siltex" OR "sio2" OR "Sipernat" OR "Snowit" OR "Spectrosil" OR "Suprasil" OR "Tridimite" OR "Tridymit" OR "Tridymite" OR "Zipax" OR "Zorbax sil" OR "a-Cristobalite" OR "a-Crystobalite" OR "a-Quartz"
	Active projects: "Acticel" OR "Admafine SO 25H" OR "Admafine SO 25R" OR "Admafine SO 32H" OR "Admafine SO-C 2" OR "Admafine SO-C 3" OR "Aerogel 200" OR "AF-SO 25R" OR "Aquafil" OR "Armsorb GKhI" OR "As 1 (silica)" OR "Belcron B 6000" OR "BF 100" OR "Borsil P" OR "Cab-O-grip II" OR "Cab-O-sperse" OR "Cabosil N 5" OR "Cabosil st-1" OR "Calofrig FJ" OR "Carplex" OR "Cataloid" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Christensenite" OR "Chromatron N Super" OR "Corning 7940" OR "CP-SilicaPLOT" OR "cristobalita" OR "CRS 1101-17" OR "CRS 1102RD8" OR "Crystalite 5K" OR "Crystalite A 1" OR "Crystalite A 2" OR "Crystalite AA" OR "Crystalite C" OR "Crystalite CRS" OR "Crystalite SS" OR "Crystalite VX-S" OR "Crystalite VX-SR" OR "Crystalite VX-X" OR "Crysvarl" OR "Denka F 90" OR "Denka FB 30" OR "Denka FB 44" OR "Denka FB 74" OR "Denka FS 30" OR "Elsil 100" OR "Elsil BF 100" OR "ENT 25,550" OR "EQ 912" OR "Extrusil" OR "Flintshot" OR "Fossil flour" OR "Fuselex" OR "Gold bond R" OR "GP 11I" OR "GP 7I" OR "HK 400" OR "Inducarb 0.5-1" OR "Keatite (SiO2)" OR "Manosil vn 3" OR "Marshalite" OR "Metacristobalite" OR "Mikrosil LM 300" OR "Mikrosil SP 10" OR "Mikrosil SP 3" OR "Millisil W 12" OR "Millisil W 3" OR "Millisil W 6" OR "Millisil W 6EST" OR "N1030" OR "Nalcast" OR "Nalco 1050" OR "Nalfloc N 1050" OR "Neosil" OR "Optocil" OR "Pigment White 27" OR "Plastorit" OR "Positive sol 130M" OR "Positive sol 232" OR "QG 100" OR "Quso 51" OR "Quso G 30" OR "Rancosil" OR "Randanite" OR "Rock crystal" OR "Santocel" OR "Sg-67" OR "Sibelco B 0012" OR "Sibelco M 10" OR "Sibelite M 3000" OR "Sibelite M 4000" OR "Sibelite M 6000" OR "Sicron F 300" OR "Sifraco C 10" OR "Sifraco C 600" OR "Sihelco B 2500" OR "Sikron 3000" OR "Sikron F 100" OR "Sikron H 200" OR "Sikron H 500" OR "Sikron H 600" OR "Sikron SF 300" OR "Sikron SF 500" OR "Sikron SF 600" OR "Sikron SF 6000" OR "Sikron SF 800" OR "Sil-Co-Sil" OR "Silane, dioxo-" OR "Silanox 101" OR "Silbond 006MST" OR "Silbond 3000MST" OR "Silbond 600EST" OR "Silbond FW 600EST" OR "Silbond FW 61EST" OR "Silbond VP 810-10/1EST" OR "Silcron F 600" OR "Silikil" OR "Silikill" OR "Sillikolloid" OR "Silver bond B" OR "Silverbond 200" OR "Silverbond 325" OR "Snowtex 30" OR "Snowtex O" OR "Stishovite (SiO2)" OR "Syton 2X" OR "TGL 16319" OR "Tokusil TPLM" OR "tridimita" OR "Ultrasil VH 3" OR "Ultrasil VN 3" OR "Vitasil 220" OR "Vitreosil IR" OR "Vulkasil" OR "W 006" OR "Wessalon" OR "WGL 300" OR "Zeofree 80"
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 6,522
- Number of records identified from other strategies: 103
- Total number of records to undergo literature screening: 6,625

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on silica:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the

second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

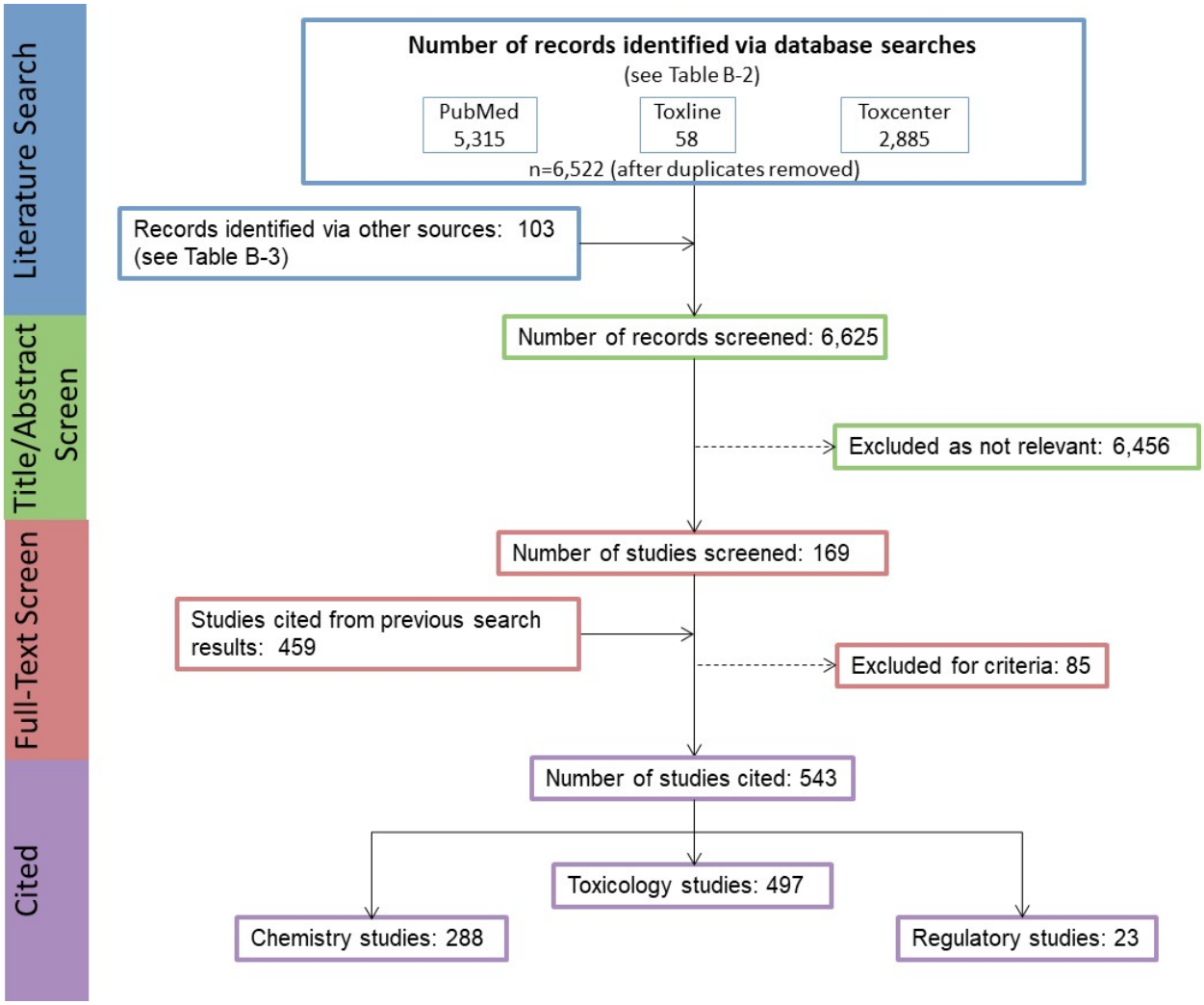
- Number of titles and abstracts screened: 6,625
- Number of studies considered relevant and moved to the next step: 169

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 169
- Number of studies cited from the search results of the pre-public draft of the toxicological profile: 459
- Total number of studies cited in the profile: 543

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2018 Literature Search Results and Screen for Silica



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

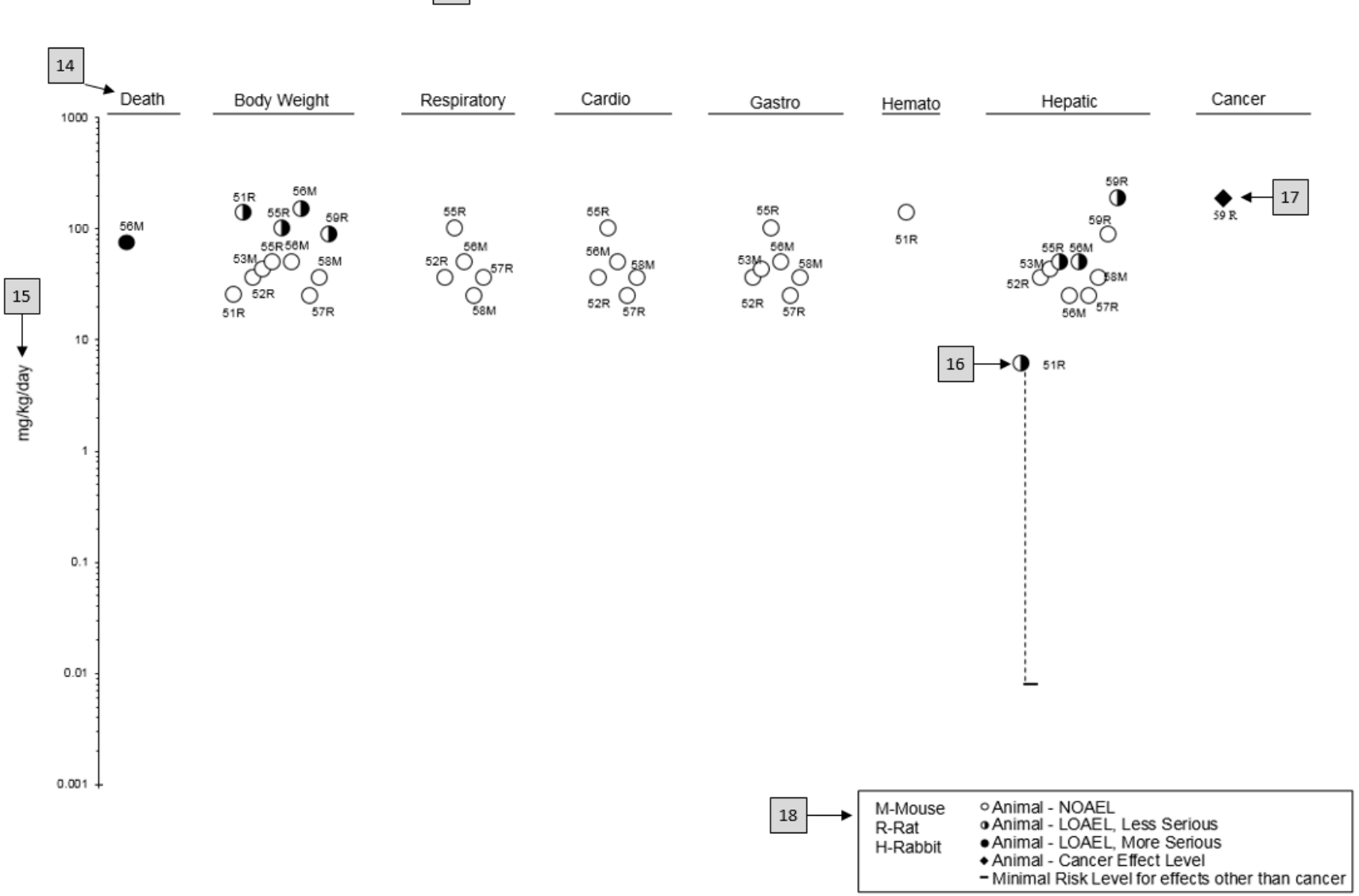
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result