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									

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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									

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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			

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					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									

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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]									

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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			

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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									

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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)

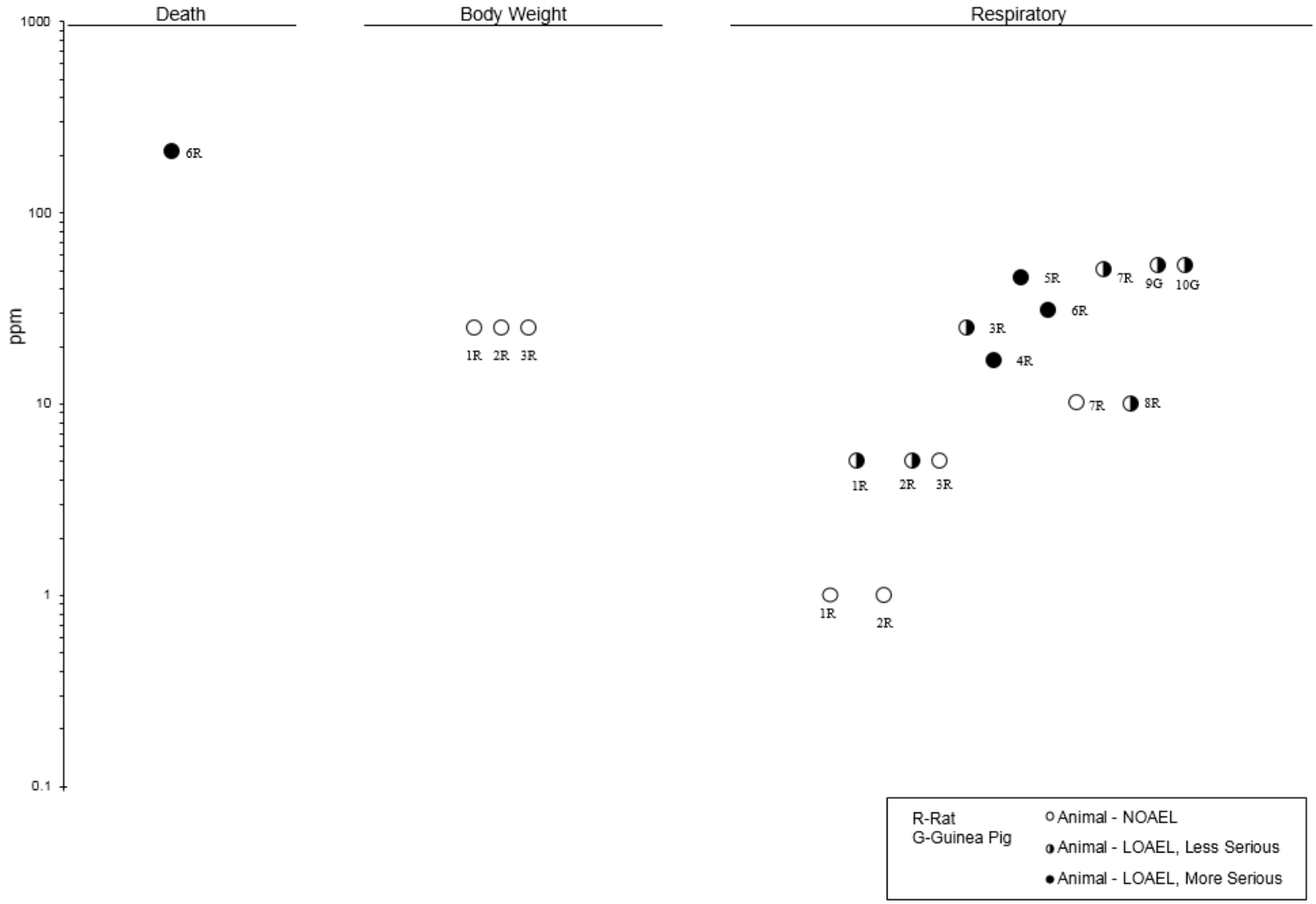


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Intermediate (15-364 days)

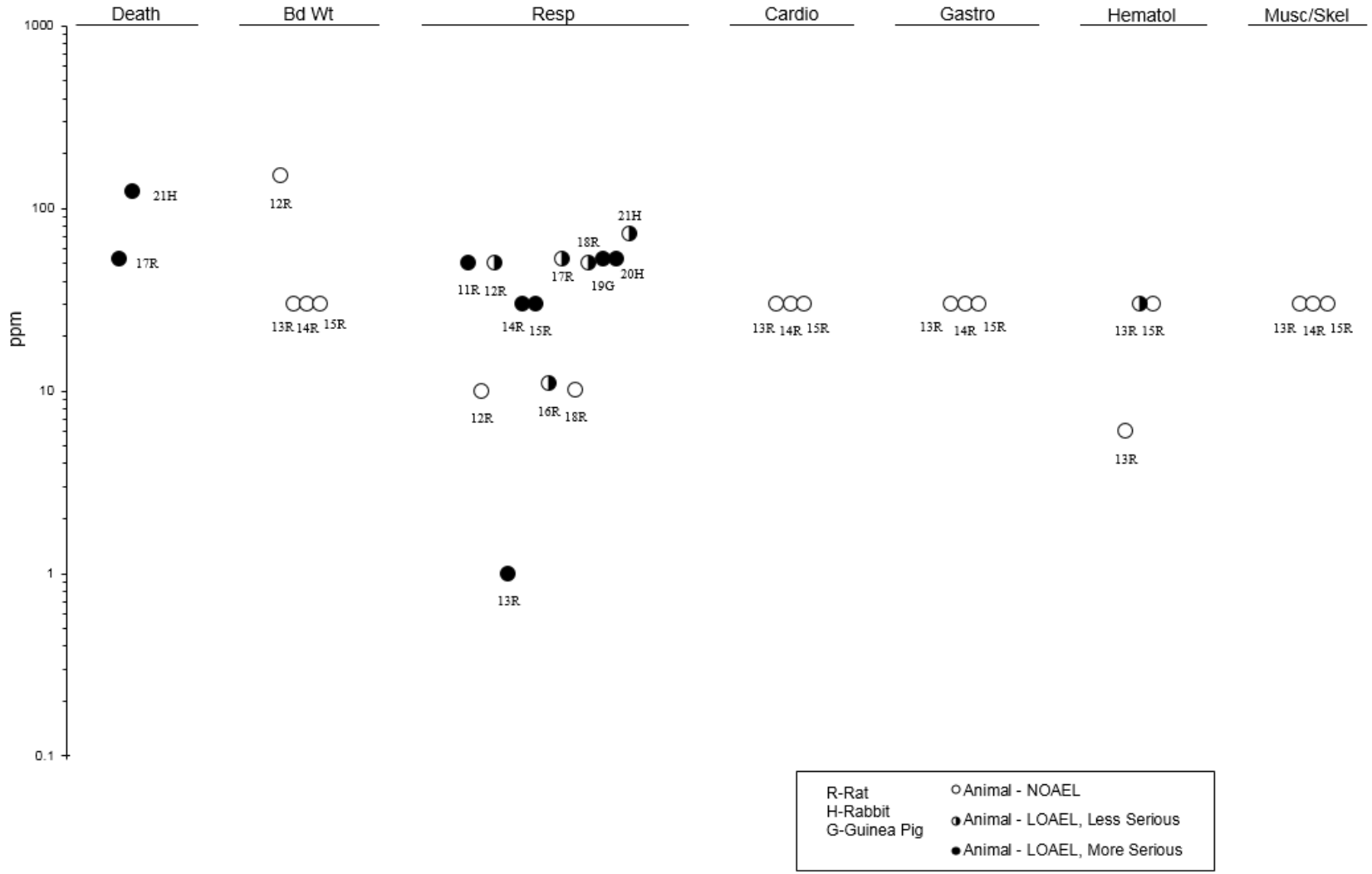


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Intermediate (15-364 days)

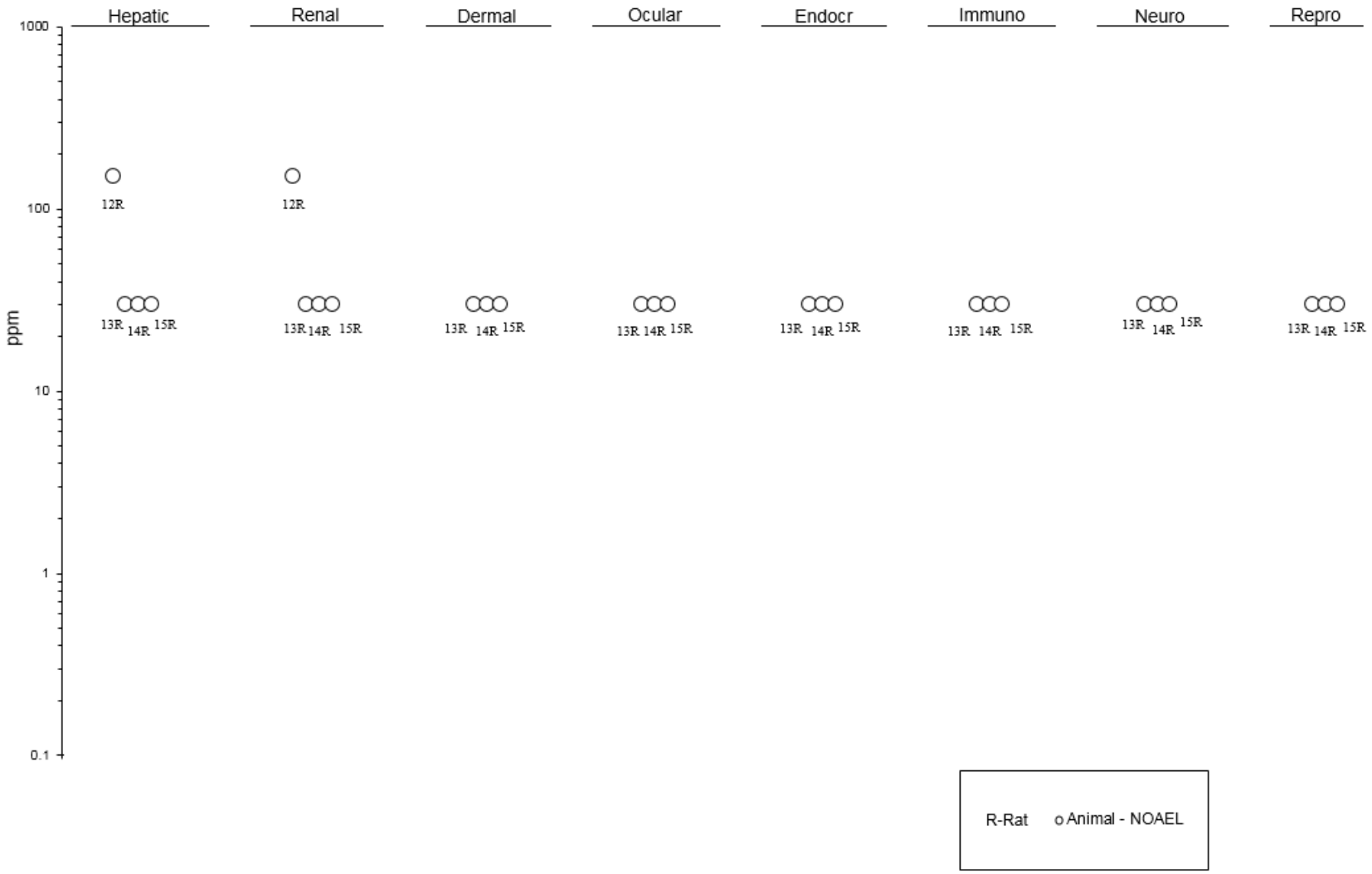


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

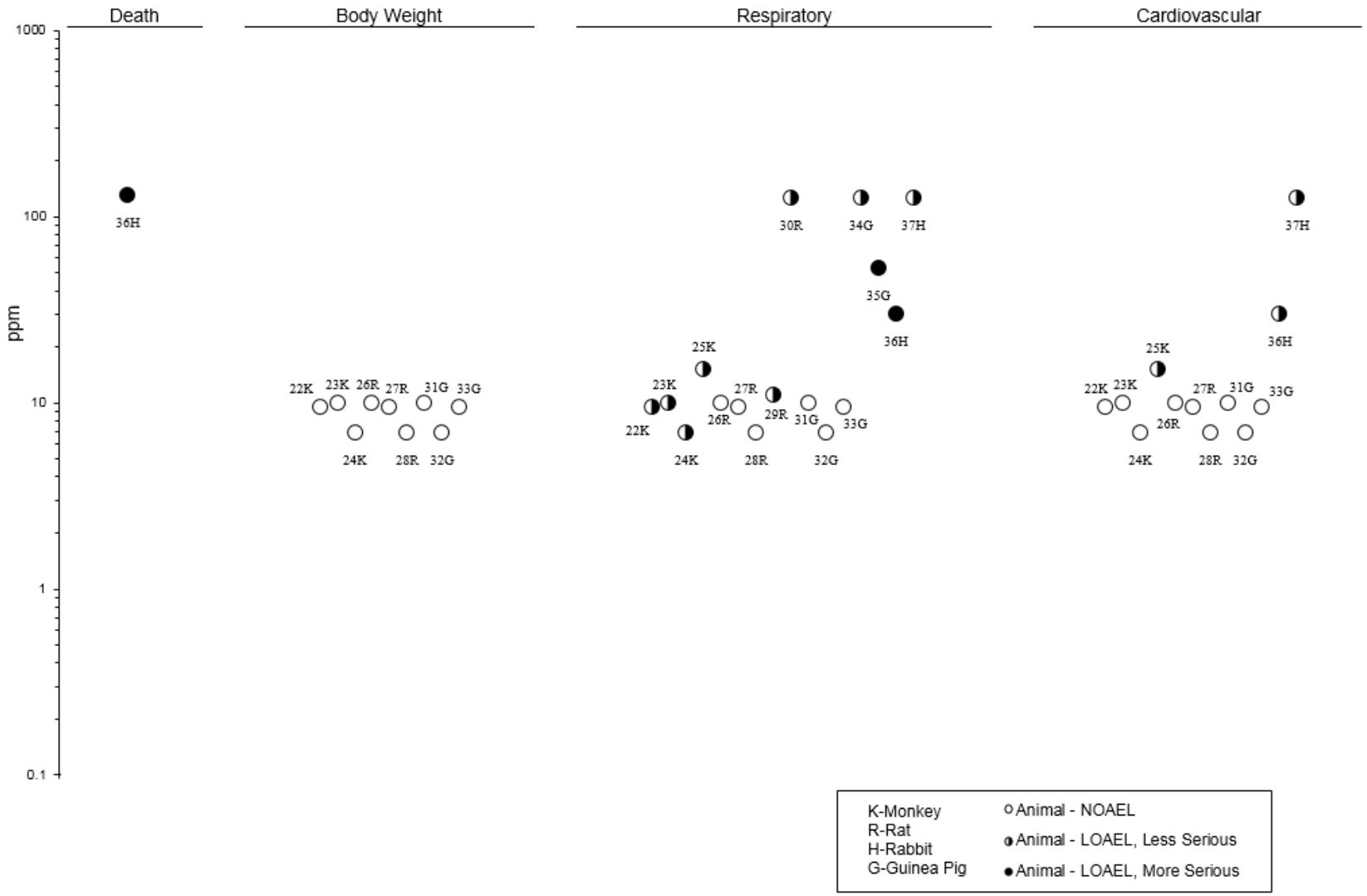


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

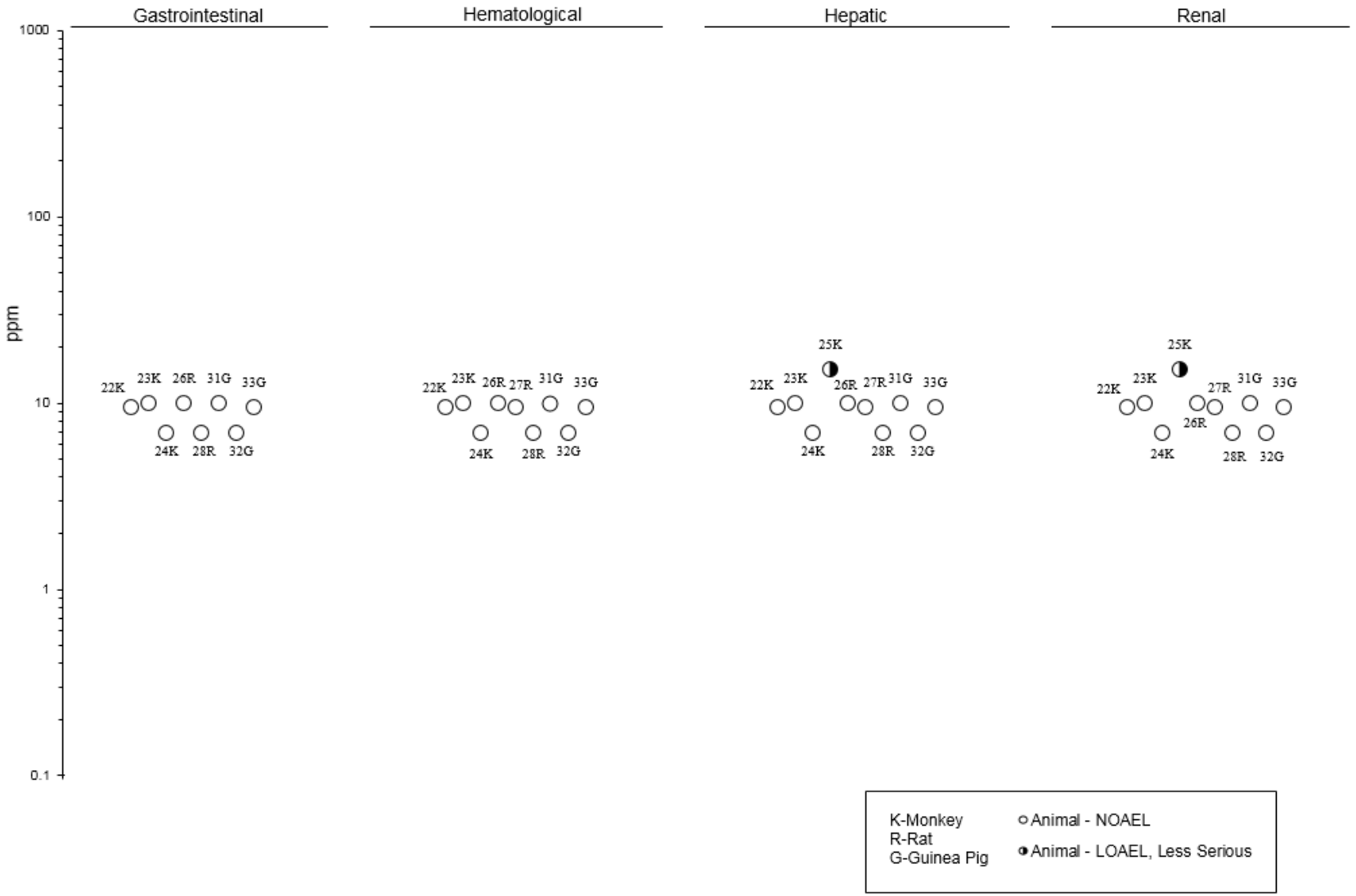


Figure 2-1. Levels of Significant Exposure to Silica – Inhalation

Chronic (≥365 days)

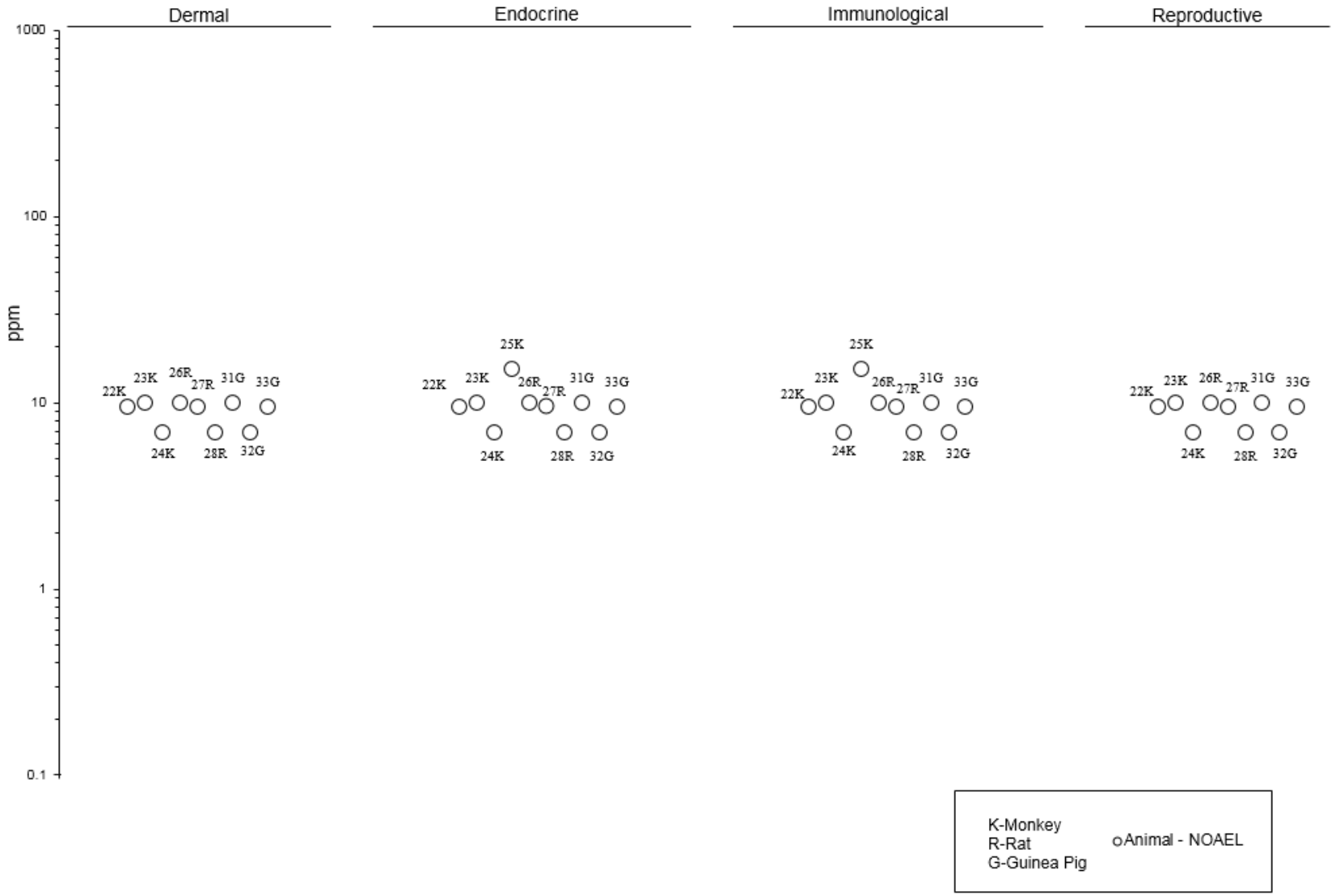


Table 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

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)

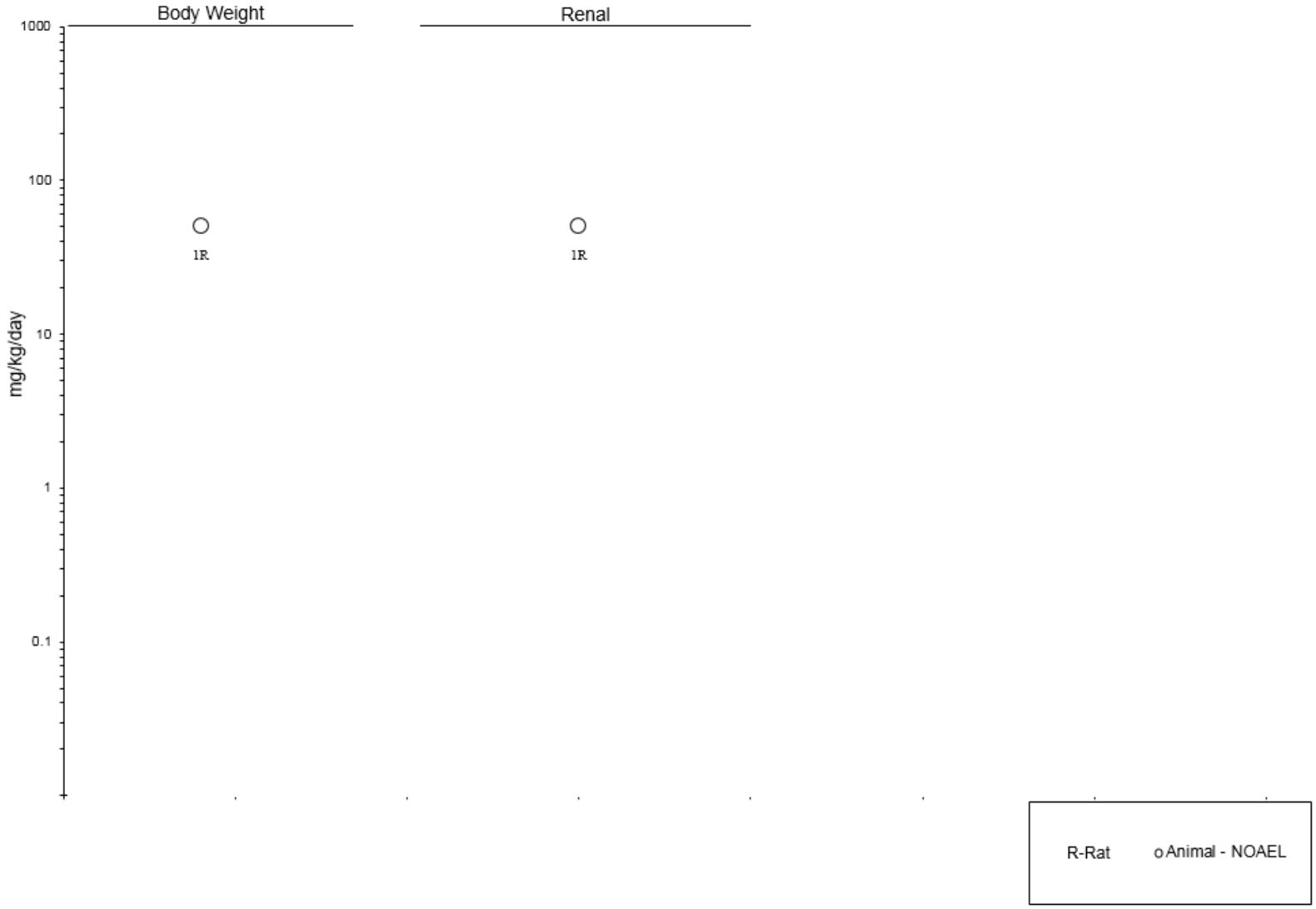


Figure 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Intermediate (15-364 days)

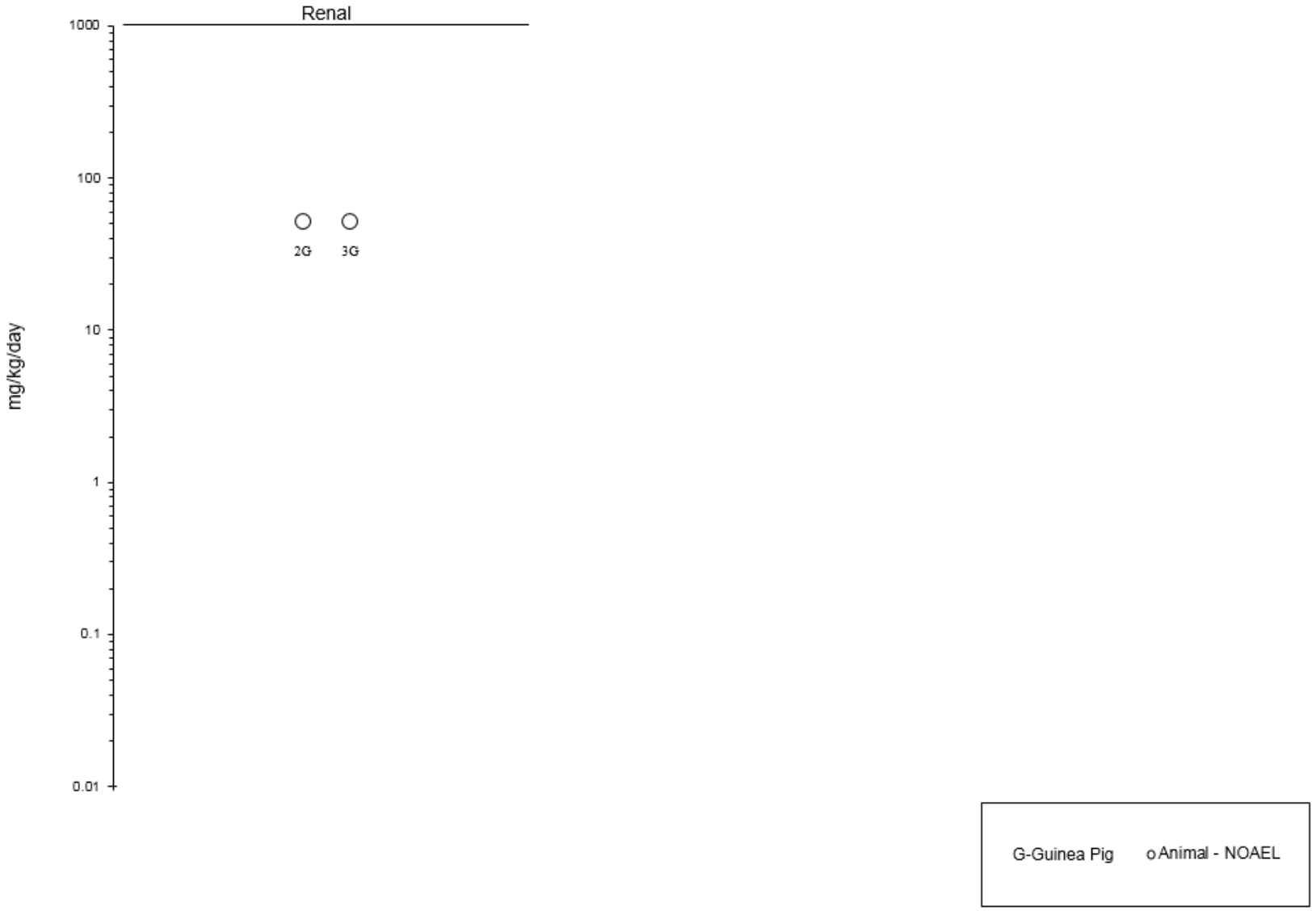


Figure 2-2. Levels of Significant Exposure to Crystalline Silica – Oral

Chronic (≥365 days)

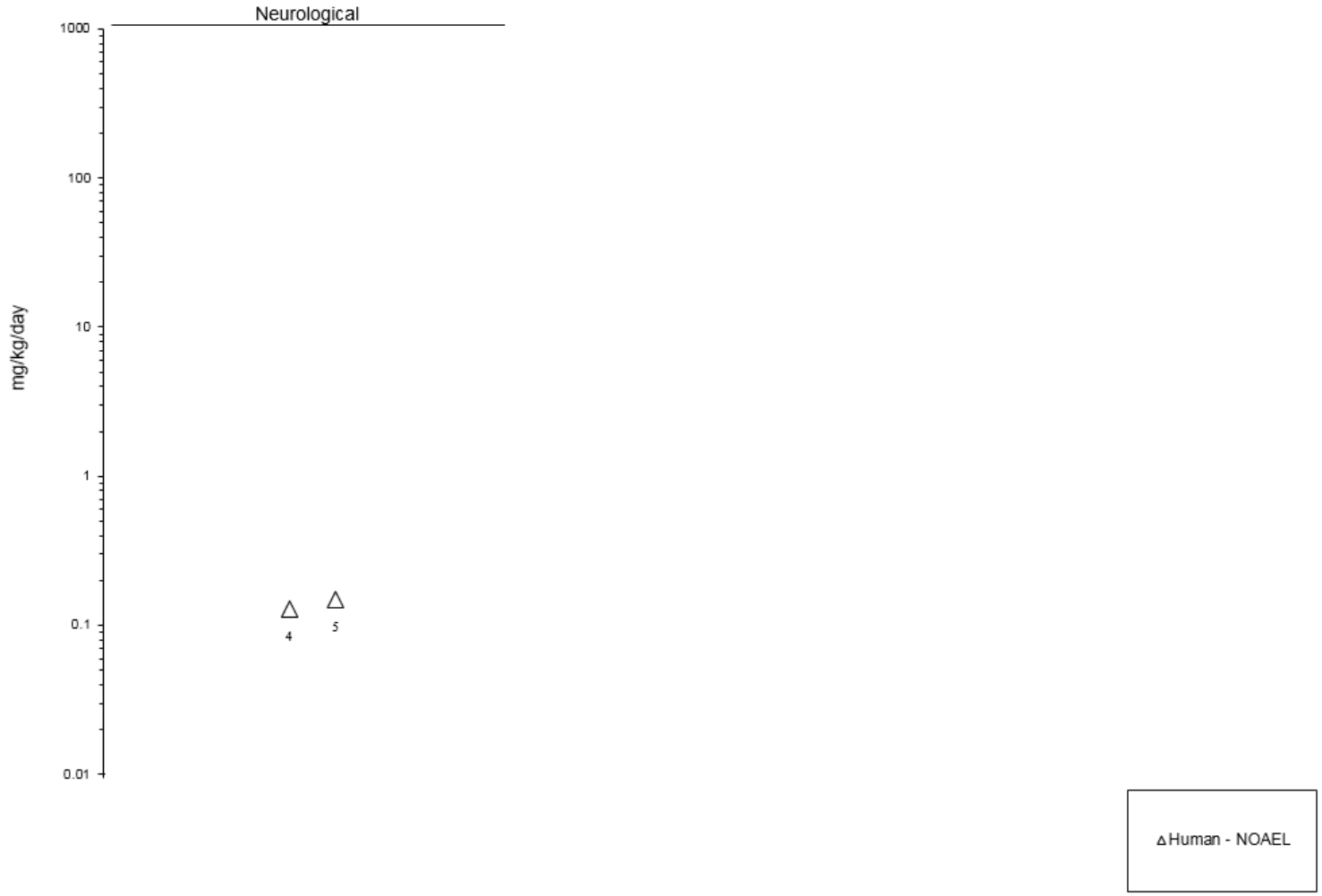


Table 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

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)

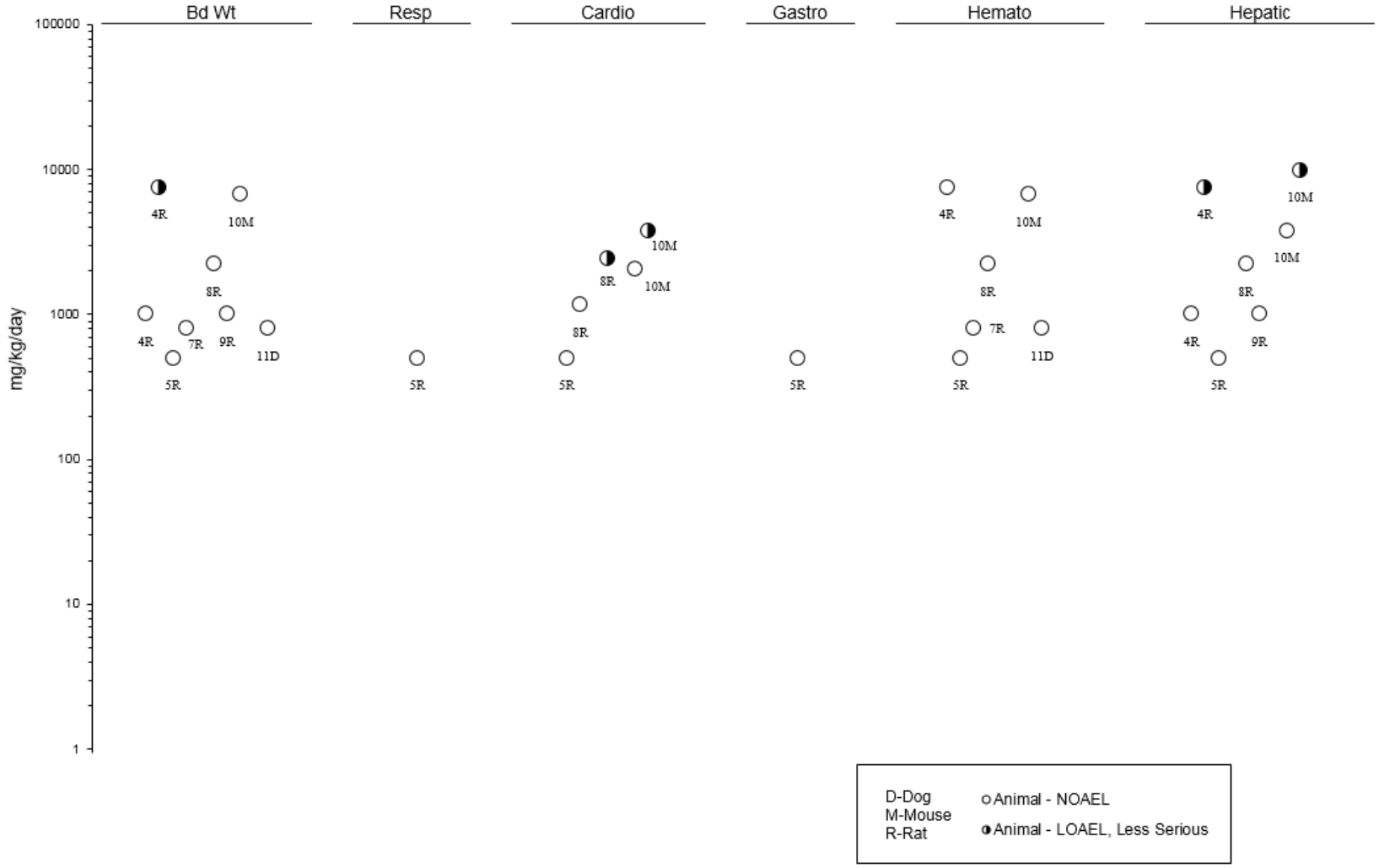


Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

Intermediate (15-364 days)

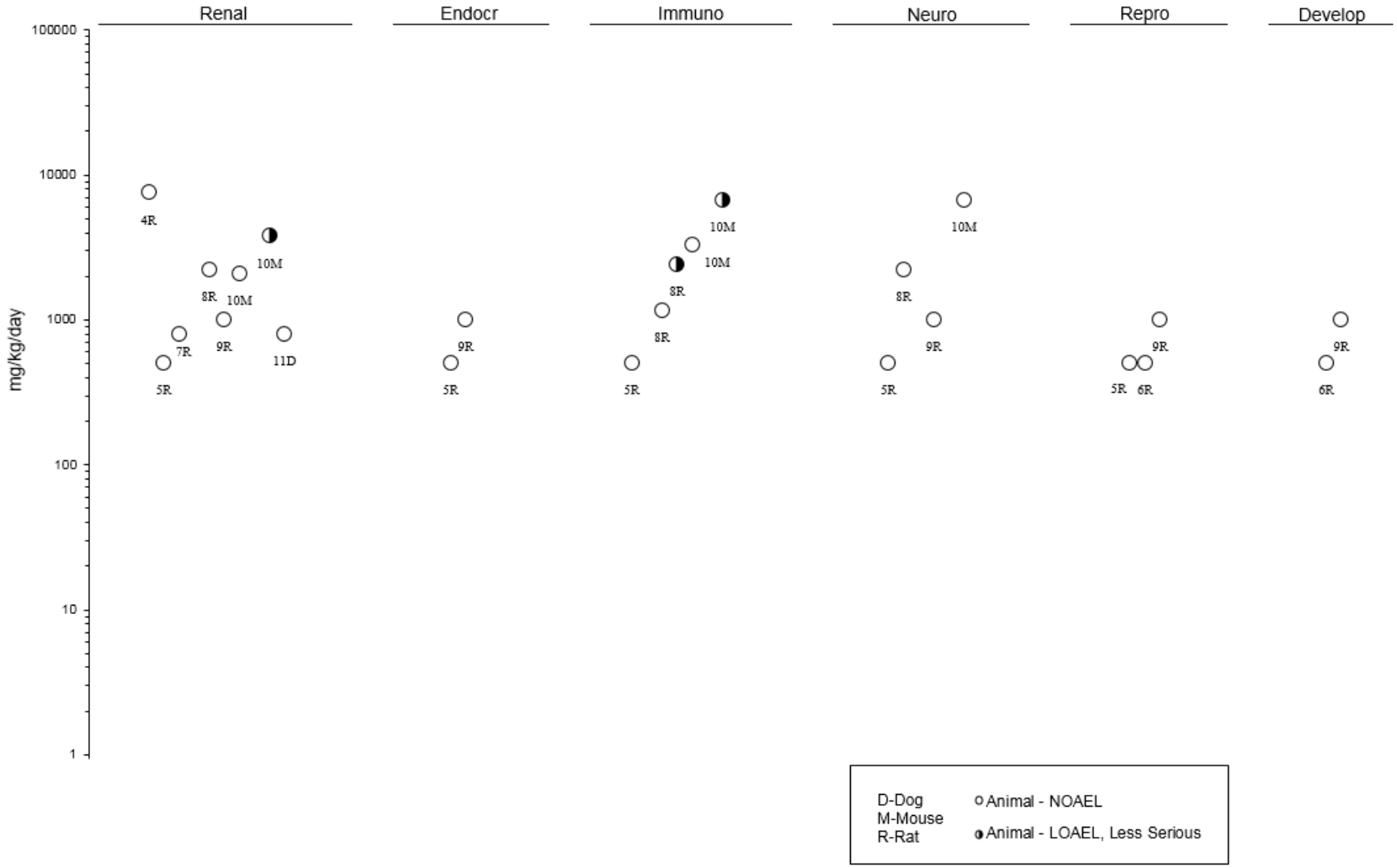
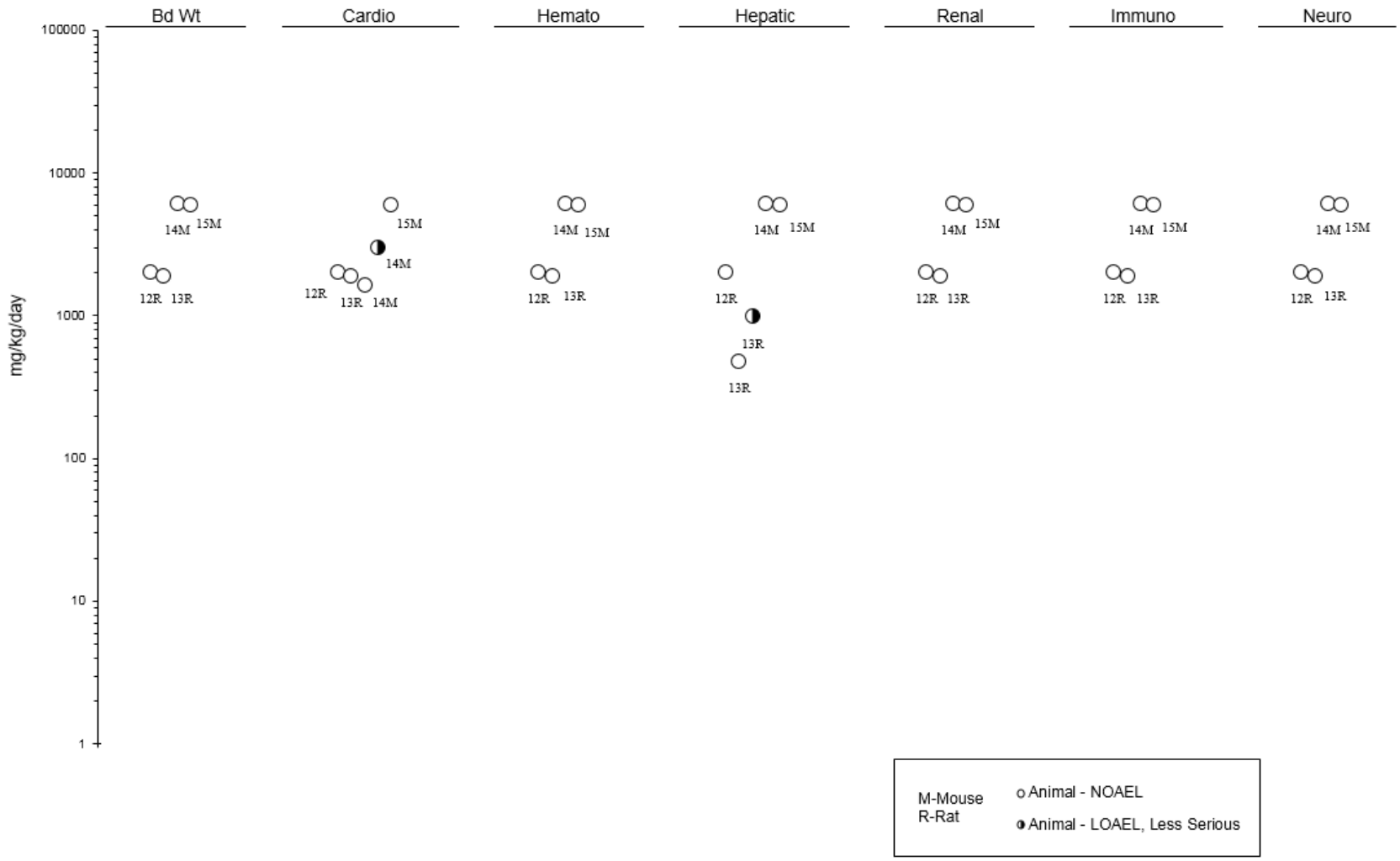


Figure 2-3. Levels of Significant Exposure to Amorphous Silica – Oral

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

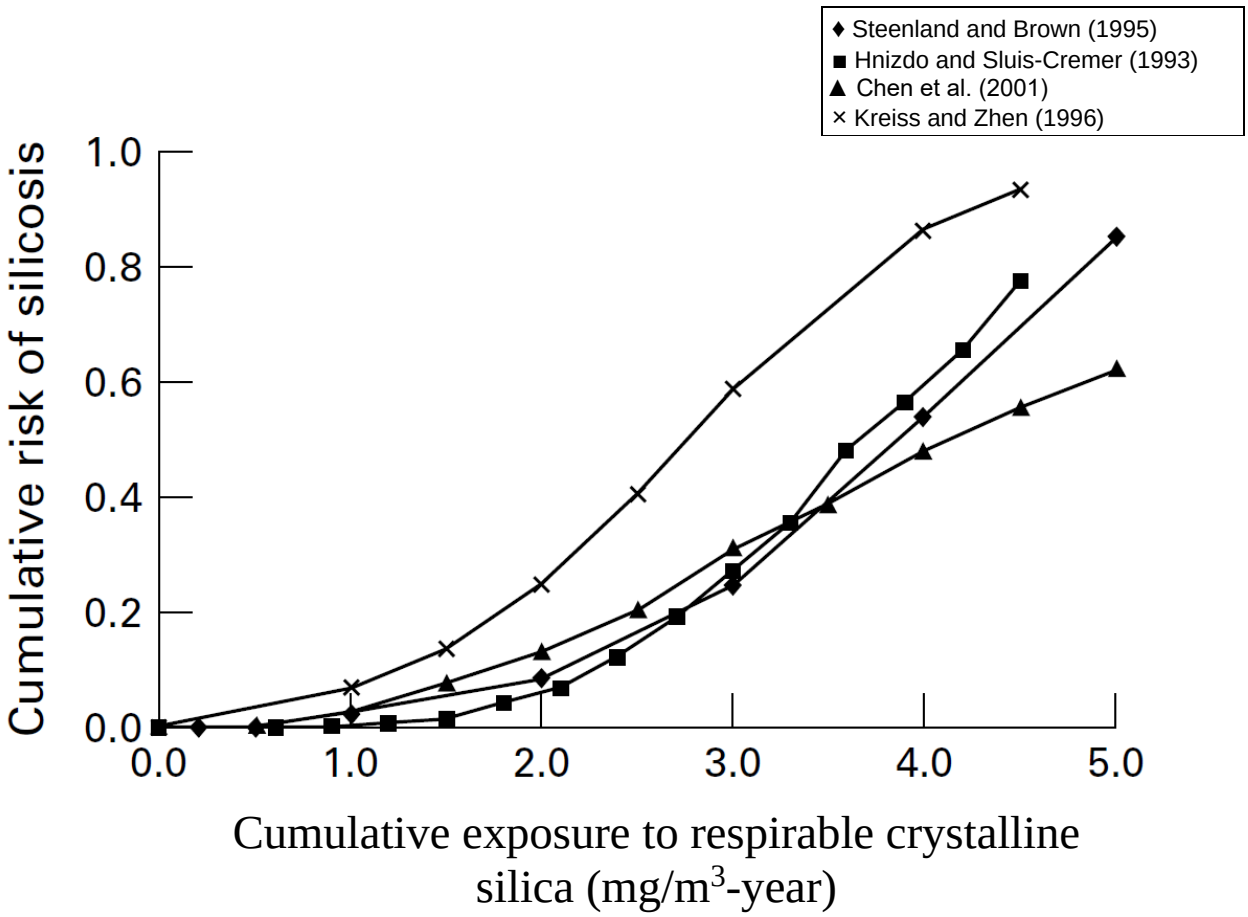
Reference	Study design and industry	Cohort and methods	Estimated cumulative exposure (mg/m^3-year)	Outcome
				Excess lifetime risk (per 1,000 workers) for all cumulative exposures for respirable c-silica concentrations of: - 0.001: 6.2 - 0.005: 17.0 - 0.010: 26.0 - 0.020: 39.0 - 0.030: 50.0 - 0.040: 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

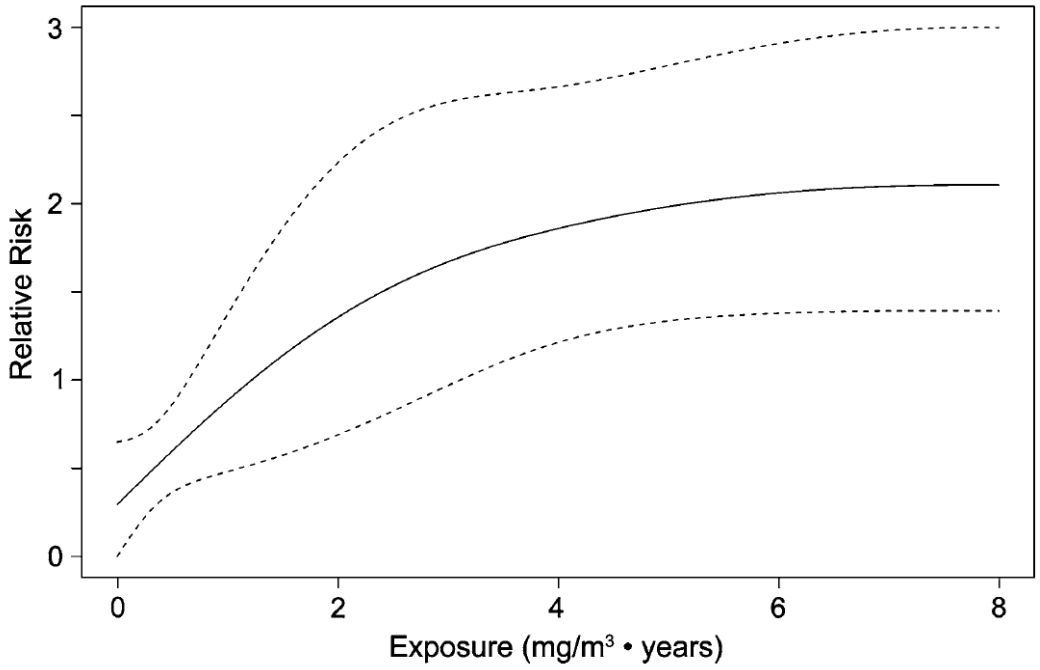
Table 2-16. Meta- or Pooled-Analysis of Exposure-Response Data for Lung Cancer in Workers Exposed to c-Silica

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

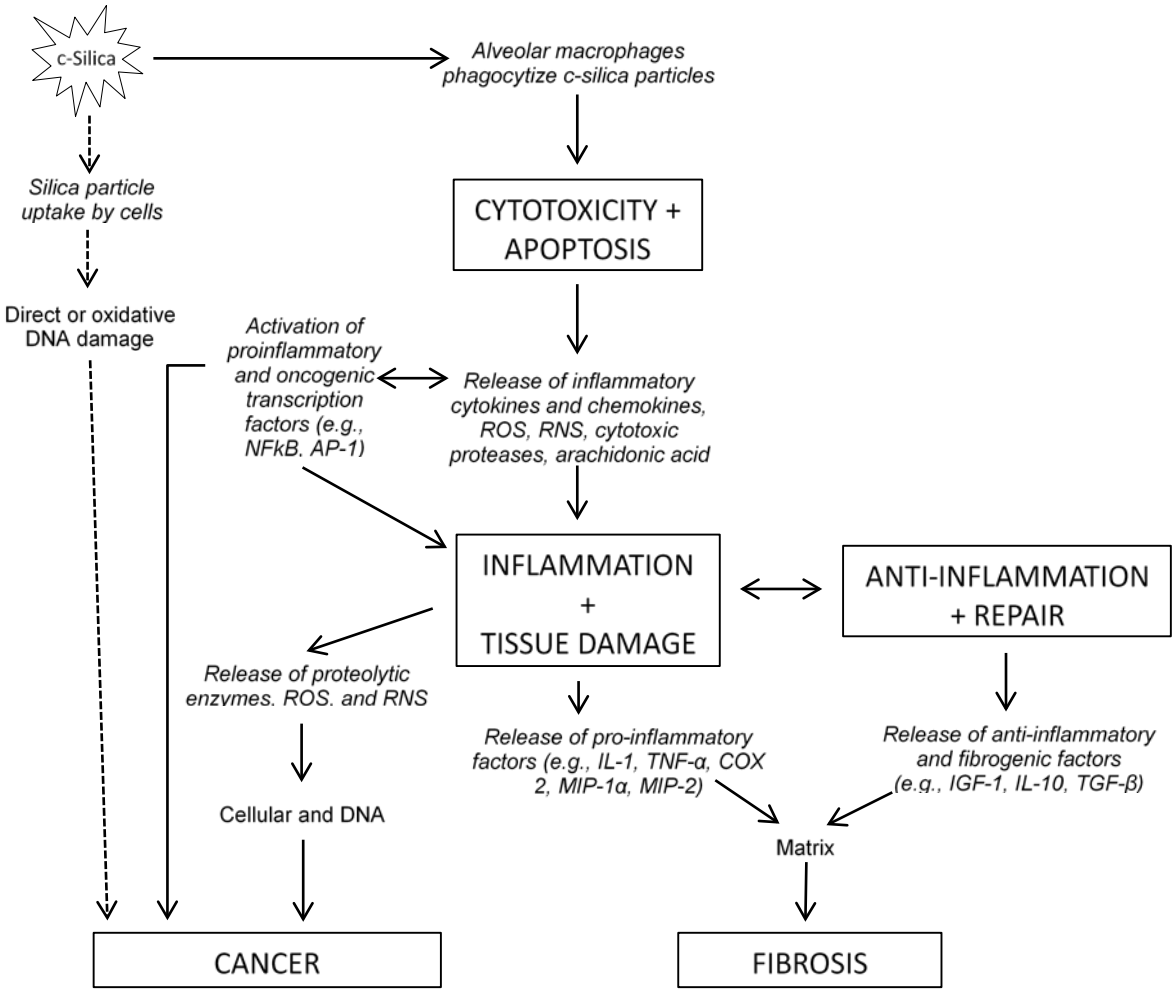
The mechanisms of toxicity for the main health effects of concern, including silicosis, COPD, lung cancer, autoimmune disease, and renal disease, for c-silica are discussed below.

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

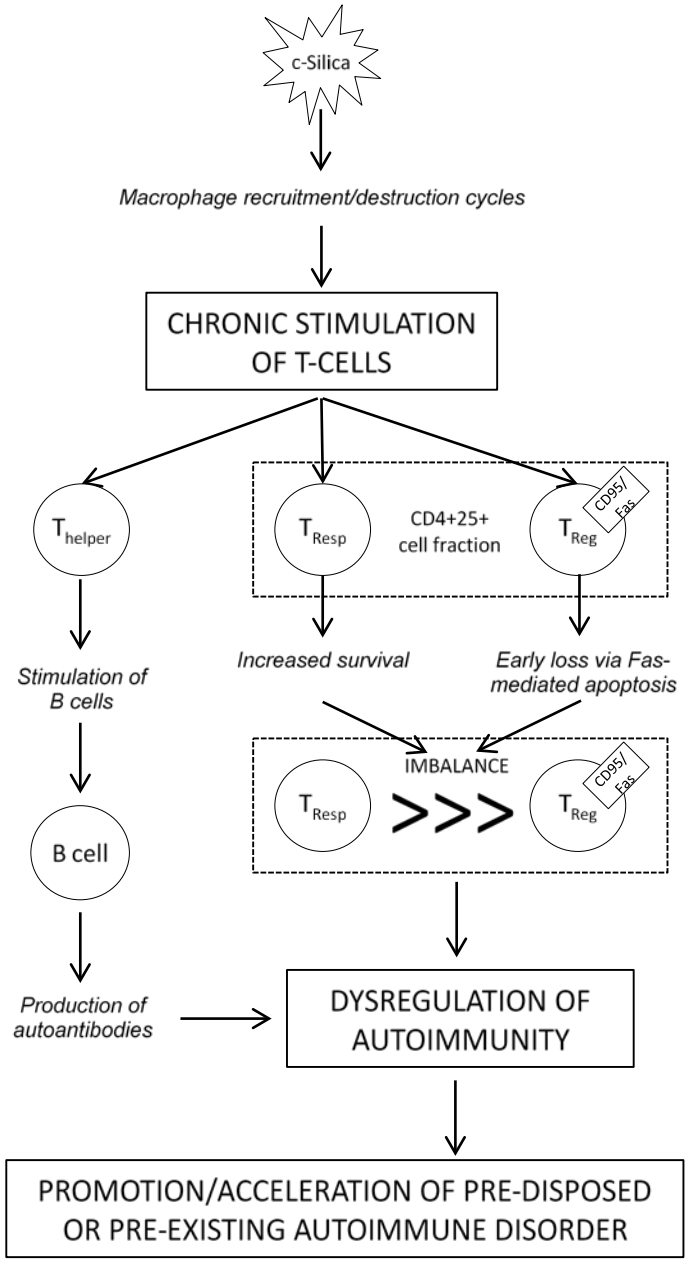
disease due to deposition of c-silica particles in the lymphatic system (transported via macrophages). In this case, macrophage destruction and recruitment cycles would occur in the lymph system (as described above in the lung), leading to stimulation of T-helper cells and B-cell production. Increased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