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NIOSH HAZARD REVIEW

Health Effects of Occupational Exposure to Respirable Crystalline Silica

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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Foreword

Silicosis is the disease most associated with crystalline silica exposure; it is incurable but preventable. This debilitating and often fatal lung disease persists worldwide despite long-standing knowledge of its cause and methods for controlling it.

This Hazard Review, *Health Effects of Occupational Exposure to Respirable Crystalline Silica*, describes published studies and literature on the health effects of occupational exposure to respirable crystalline silica among workers in the United States and many other countries. The review indicates a significant risk of chronic silicosis for workers exposed to respirable crystalline silica over a working lifetime at the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL), the Mine Safety and Health Administration (MSHA) PEL, or the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL). In addition to the risk of silicosis, epidemiologic studies indicate that workers exposed to respirable crystalline silica have an increased risk of developing lung cancer, pulmonary tuberculosis, and airways diseases. The latest scientific information also indicates possible associations of occupational exposure to silica dust with various other adverse health effects.

Until improved sampling and analytical methods are developed for respirable crystalline silica, NIOSH will continue to recommend an exposure limit of 0.05 mg/m^3 as a time-weighted average (TWA) for up to a 10-hr workday during a 40-hr workweek. NIOSH also recommends substituting less hazardous materials for crystalline silica when feasible, using appropriate respiratory protection when source controls cannot keep exposures below the REL, and making medical examinations available to exposed workers.

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Abstract

Occupational exposures to respirable crystalline silica are associated with the development of silicosis, lung cancer, pulmonary tuberculosis, and airways diseases. These exposures may also be related to the development of autoimmune disorders, chronic renal disease, and other adverse health effects. Recent epidemiologic studies demonstrate that workers have a significant risk of developing chronic silicosis when they are exposed to respirable crystalline silica over a working lifetime at the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL), the Mine Safety and Health Administration (MSHA) PEL, or the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL).

This NIOSH Hazard Review (1) examines the health risks and diseases associated with occupational exposures to respirable crystalline silica, (2) discusses important findings of recent epidemiologic studies, (3) provides the reader with sources of more comprehensive information about health effects and experimental studies, (4) describes current sampling and analytical methods and their limitations for assessing occupational exposures to respirable crystalline silica, and (5) suggests many areas for further research.

Current sampling and analytical methods used to evaluate occupational exposure to respirable crystalline silica do not meet the accuracy criterion needed to quantify exposures at concentrations below the NIOSH REL of 0.05 mg/m^3 as a time-weighted average (TWA) for up to a 10-hr workday during a 40-hr workweek. Until improved sampling and analytical methods are developed for respirable crystalline silica, NIOSH will continue to recommend an exposure limit of 0.05 mg/m^3 to reduce the risk of developing silicosis, lung cancer, and other adverse health effects. NIOSH also recommends minimizing the risk of illness that remains for workers exposed at the REL by substituting less hazardous materials for crystalline silica when feasible, by using appropriate respiratory protection when source controls cannot keep exposures below the NIOSH REL, and by making medical examinations available to exposed workers.

Executive Summary

Occupational exposures to respirable crystalline silica occur in a variety of industries and occupations because of its extremely common natural occurrence and the wide uses of materials and products that contain it. At least 1.7 million U.S. workers are potentially exposed to respirable crystalline silica [NIOSH 1991], and many are exposed to concentrations that exceed limits defined by current regulations and standards.

Silicosis, usually a nodular pulmonary fibrosis, is the disease most associated with exposure to respirable crystalline silica. Although the reported mortality associated with silicosis has declined over the past several decades, many silicosis-associated deaths still occur (nearly 300 deaths were reported each year during the period 1992–1995) [NIOSH 1996a; Althouse 1998]. In addition, the number of silicosis-associated deaths among persons aged 15 to 44 has not declined substantially [CDC 1998a,b]. An unknown number of workers also continue to die from silica-related diseases such as pulmonary tuberculosis (TB), lung cancer, and scleroderma. The number of cases of silicosis and silica-related diseases in the United States today is unknown.

Symptoms of acute silicosis, another form of silicosis, may develop shortly after exposure to high concentrations of respirable crystalline silica. Epidemiologic studies focus on chronic silicosis, which develops years after exposure to relatively low concentrations of respirable crystalline silica. Epidemiologic studies have found that chronic silicosis may develop or progress even after occupational exposure has ceased [Hessel et al. 1988; Hnizdo and Sluis-Cremer 1993; Hnizdo and Murray 1998; Ng et al. 1987; Kreiss and Zhen 1996; Miller et al. 1998]. Over a 40- or 45-year working lifetime, workers have a significant chance (at least 1 in 100) of developing radiographic silicosis when exposed to respirable crystalline silica at the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL), the Mine Safety and Health Administration (MSHA) PEL, or the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL).*

Silicosis may be complicated by severe mycobacterial or fungal infections. About half of these are caused by *Mycobacterium tuberculosis* and result in TB. Epidemiologic studies have firmly established that silicosis is a risk factor for developing TB.

The carcinogenicity of crystalline silica in humans has been strongly debated in the scientific community. In 1996, the International Agency for Research on Cancer (IARC) reviewed the published experimental and epidemiologic studies of cancer in animals and workers exposed to respirable crystalline silica and concluded that there was "sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources" [IARC 1997]. In the same year, directors of the American Thoracic Society (ATS) adopted an official statement that described the adverse health effects of exposure to crystalline silica, including lung cancer [ATS 1997]. The ATS found that "the available data support the conclusion that silicosis produces increased risk

*See appendix for the OSHA and MSHA PELs. The NIOSH REL is 0.05 mg/m^3 as a time-weighted average (TWA) for up to a 10-hr workday during a 40-hr workweek.

for bronchogenic carcinoma." However, the ATS noted that less information was available for lung cancer risks among silicotics who had never smoked and for silica-exposed workers who did not have silicosis. They also stated that it was "less clear" whether silica exposure was associated with lung cancer in the absence of silicosis. NIOSH has reviewed the studies considered by IARC and ATS, and NIOSH concurs with the conclusions of IARC [1997] and the ATS [1997]. These conclusions agree with NIOSH testimony to OSHA, in which NIOSH recommended that crystalline silica be considered a potential occupational carcinogen [54 Fed. Reg.* 2521 (1989)]. Further research is needed to determine the exposure-response relationship between lung cancer in nonsmokers and occupational silica dust exposure and to determine why lung cancer risks appear to be higher in workers with silicosis. The cellular mechanisms for development of lung cancer after crystalline silica exposure have been explored in many experimental studies and are not yet fully understood.

Statistically significant excesses of mortality from stomach or gastric cancer have been reported in various occupational groups exposed to crystalline silica. However, no conclusion about an association has been reached because most studies did not adjust for the effects of confounding factors or assess an exposure-response relationship for crystalline silica. The same problem exists for the infrequent reports of statistically significant numbers of excess deaths or cases of other nonlung cancers in silica-exposed workers.

Occupational exposure to respirable crystalline silica is associated with chronic obstructive pulmonary disease, including bronchitis and emphysema. The results of some epidemiologic studies suggest that these diseases may be less frequent or absent in nonsmokers. Exposure to respirable crystalline silica is not associated with asthma.

Significant increases in mortality from nonmalignant respiratory disease (a broad category that can include silicosis and other pneumoconioses, chronic bronchitis, emphysema, asthma, and other related respiratory conditions) have been reported for silica-exposed workers [Checkoway et al. 1997, 1993; Chen et al. 1992; Cherry et al. 1998; Brown et al. 1986; Costello and Graham 1988; Costello et al. 1995; Costello 1983; Steenland and Brown 1995b; Steenland and Beaumont 1986; Thomas and Stewart 1987; Thomas 1990] and silicotics [Goldsmith et al. 1995; Brown et al. 1997; Rosenman et al. 1995].

Many case reports have been published about autoimmune diseases or autoimmune-related diseases in workers exposed to crystalline silica or workers with silicosis. In addition, several recent epidemiologic studies reported statistically significant numbers of excess cases or deaths from known autoimmune diseases or immunologic disorders (scleroderma, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis), chronic renal disease, and subclinical renal changes. The pathogenesis of autoimmune and renal diseases in silica-exposed workers is not clear.

Various other health effects (such as hepatic or hepatosplenic silicosis, extrapulmonary deposition of silica particles, liver granulomas, hepatic porphyria, cutaneous silica granulomas, pulmonary alveolar proteinosis, podoconiosis, and dental abrasion) have been reported in studies of silica-exposed workers, but these effects have not been studied in depth with epidemiologic methods.

This Hazard Review also provides an abbreviated review of experimental research studies conducted to identify the molecular mechanisms responsible for the development of

*Federal Register. See Fed. Reg. in references.

silicosis and lung cancer. The results of these studies indicate the need for (1) additional long-term carcinogenesis studies in animals to determine dose-response relationships and (2) in vivo and in vitro studies to develop effective cellular and molecular models of carcinogenesis.

Although a large body of published literature describes the health effects of crystalline silica, some areas require further research. Many uncertainties exist, including (1) mechanisms and the influence of particle characteristics on development of disease; (2) toxicity and pathogenicity of nonquartz crystalline silica, silica substitutes, and dust mixtures; (3) translocation of particles from the lung; and (4) dose/exposure-response relationships in animals and in humans. In addition, further information is needed about (1) methods for reducing dust exposures in a wide variety of industries and the feasibility of implementing such methods, (2) methods for effectively communicating to workers the dangers of inhaling silica dust and the importance of using appropriate control technologies and other protective measures, and (3) exposure sampling and analytical methods that will allow quantification of crystalline silica at low airborne concentrations (currently these techniques do not meet the accuracy criterion needed to quantify exposures at concentrations below the NIOSH REL).

Until improved sampling and analytical methods are developed for respirable crystalline silica, NIOSH will continue to recommend an exposure limit of 0.05 mg/m^3 to reduce the risk of developing silicosis, lung cancer, and other adverse health effects. NIOSH also recommends minimizing the risk of illness that remains for workers exposed at the REL by substituting less hazardous materials for crystalline silica when feasible, by using appropriate respiratory protection when source controls cannot keep exposures below the NIOSH REL, and by making medical examinations available to exposed workers.

Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AMG	alpha-1-microglobulin
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BMG	beta-1-microglobulin
BMI	body mass index
°C	degree(s) Celsius
CA	chromosomal aberration(s)
cc	cubic centimeter
CDC	Centers for Disease Control and Prevention
CEN	European Standardization Committee
CFR	Code of Federal Regulations
CI	confidence interval
cm	centimeter(s)
COC	census occupation code
COPD	chronic obstructive pulmonary disease
Cu	copper
CV	coefficient of variation
$\overline{CV}$	pooled coefficient of variation
CWP	coal workers' pneumoconiosis
DE	diatomaceous earth
DLCO	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
EPA	U.S. Environmental Protection Agency
°F	degree(s) Fahrenheit
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity

g	gram(s)
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hprt	hypoxanthine-guanine phosphoribosyl transferase
hr	hour(s)
HSE	Health and Safety Executive (United Kingdom)
HVLV	high-velocity/low-volume
IARC	International Agency for Research on Cancer
ICD–9	International Classification of Diseases, 9th edition
Ig	immunoglobulin
IGLV	immunoglobulin lambda-variable chain
ILO	International Labour Organization
IR	infrared absorption
ISO	International Organization for Standardization
K_α	electron ionization energy
KBr	potassium bromide
kv	kilovolt(s)
L	liter(s)
LOD	limit of detection
m	meter(s)
mA	milliamp(s)
MDHS	Methods for the Determination of Hazardous Substances (Health and Safety Executive, United Kingdom)
mg	milligram(s)
$mg/m^3 \cdot yr$	milligrams per cubic meter times years
min	minute(s)
ml	milliliter(s)
mm	millimeter(s)
mppcf	million particles per cubic foot
MSHA	Mine Safety and Health Administration
NAG	beta-N-acetyl-D-glucosaminidase

NIOSH	National Institute for Occupational Safety and Health
NIST	National Institute of Standards and Technology
NMRD	nonmalignant respiratory disease
NOES	National Occupational Exposure Survey
NOHSM	National Occupational Health Survey of Mining
NOMS	U.S. National Occupational Mortality Surveillance
NTM	nontuberculous mycobacteria
OR	odds ratio
OSHA	Occupational Safety and Health Administration
P	probability
PAP	pulmonary alveolar proteinosis
PAT	proficiency analytical testing
PDGF	platelet-derived growth factor
PEL	permissible exposure limit
PMR	proportionate mortality ratio
ppm	parts per million
PVC	polyvinyl chloride
RDS	respirable dust standard
REL	recommended exposure limit
RF	radio frequency
RFLP	restriction fragment length polymorphism
ROS	reactive oxygen species
RSD	relative standard deviation
$\overline{\text{RSD}}$	pooled relative standard deviation
SCE	sister chromatid exchange
SCG	single cell gel/comet
SIC	standard industrial classification
SiO_2	silicon dioxide
SIR	standardized incidence ratio
SMR	standardized mortality ratio

SRR	standardized rate ratio
TGF	transforming growth factor
TB	pulmonary tuberculosis
THF	tetrahydrofuran
TWA	time-weighted average
U.K.	United Kingdom
U.S.	United States
VC	vital capacity
WASP	Workplace Analysis Scheme for Proficiency
WHO	World Health Organization
wk	week(s)
XRD	X-ray diffraction
yr	year(s)
µg	microgram(s)
µm	micrometer(s)
%	percent

Glossary

Aerodynamic diameter: The diameter of a sphere with a density of 1 g/cm^3 and with the same velocity (due to gravity) as the particle of interest [EPA 1996]. Particles of a given aerodynamic diameter move within the air spaces of the respiratory system identically, regardless of density or shape [NIOSH 1995a].

Chronic obstructive pulmonary disease (COPD): Includes airways diseases such as asthma, chronic bronchitis, and emphysema and is characterized by airways dysfunction [Becklake 1992].

Clearance: The translocation and removal of deposited particles from the respiratory tract.

Concentration: The amount of a substance (e.g., dust particles) contained per unit volume of air.

Confidence interval (CI), confidence limits: A range of values (determined by the degree of presumed random variability in the data) within which the value of a parameter (e.g., a mean or relative risk) is believed to lie with the specified level of confidence. The boundaries of a confidence interval are the confidence limits [Last 1988]. These include the lower confidence limit and the upper confidence limit.

Crystalline silica (or free silica): Silicon dioxide (SiO_2). "Crystalline" refers to the orientation of SiO_2 molecules in a fixed pattern as opposed to a nonperiodic, random molecular arrangement defined as amorphous. The three most common crystalline forms of silica encountered in the workplace environment are quartz, tridymite, and cristobalite [NIOSH 1974].

ILO category: The determination of profusion of small opacities observed by reading chest radiographs according to classification of pneumoconioses guidelines developed by the International Labour Organization (ILO). The latest classification guidelines were published by the International Labour Office in 1980 [ILO 1980].

Incidence: The frequency with which new cases of a disease occur in a given time period.

Incidence rate: The rate at which new events occur in a population. The number of new events (e.g., new cases of a disease diagnosed or reported during a defined period) is divided by the number of persons in the population in which the cases occurred [Last 1988].

Inhalable dust: The particulate mass fraction of dust in the work environment that can be inhaled and deposited anywhere in the respiratory tract.

Nontuberculous mycobacteria: Mycobacteria species other than the *Mycobacterium tuberculosis* complex (e.g., *Mycobacterium avium* complex).

Prevalence: The number of disease cases in a specific population at a particular time [Last 1988].

Prevalence rate (ratio): The total number of all individuals with an attribute or disease at a given time or during a given period divided by the population at risk of having the attribute or disease at this point in time or midway through the period [Last 1988].

Proportionate mortality ratio (PMR): Ratio of the proportion of deaths from a specific cause in an exposed population compared with the corresponding ratio in the nonexposed population. For example, the proportion of deaths from disease X in the exposed population could be compared with the proportion of deaths from disease X in the nonexposed population [NIOSH 2000].

Quartz: Crystalline silicon dioxide (SiO_2) not chemically combined with other substances and having a distinctive physical structure.

Respirable crystalline silica: That portion of airborne crystalline silica that is capable of entering the gas-exchange regions of the lungs if inhaled; by convention, a particle-size-selective fraction of the total airborne dust; includes particles with aerodynamic diameters less than approximately 10 µm and has a 50% deposition efficiency for particles with an aerodynamic diameter of approximately 4 µm.

Sarcoidosis: A rare multisystem granulomatous disease characterized by alterations in the immune system [Fanburg 1992].

Scleroderma (progressive systemic sclerosis): A rare multisystem disorder characterized by inflammatory, vascular, and fibrotic changes usually involving the skin, blood vessels, joints, and skeletal muscle [Archer and Gordon 1996].

Standardized mortality ratio: The ratio of the number of deaths observed in the study population to the number of deaths expected if the study population had the same rate structure as the standard population [Last 1988].

Standardized rate ratio: A rate ratio in which the numerator and denominator rates have been standardized to the same (standard) population distribution [Last 1988].

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1 Introduction

1.1 Definition of Crystalline Silica

Silica refers to the chemical compound silicon dioxide (SiO_2), which occurs in a crystalline or noncrystalline (amorphous) form. Crystalline silica may be found in more than one form (polymorphism). The polymorphic forms of crystalline silica are alpha quartz, beta quartz, tridymite, cristobalite, keatite, coesite, stishovite, and moganite [Ampian and Virta 1992; Heaney 1994; Guthrie and Heaney 1995]. Each polymorph is unique in its spacing, lattice structure, and angular relationship of the atoms. In nature, the alpha (or low) form of quartz is the most common [Virta 1993]. This form is so abundant that the term *quartz* is often used in place of the general term *crystalline silica* [BOM 1992; Virta 1993]. Quartz is a common component of soil and rocks; consequently, workers are potentially exposed to quartz dust in many occupations and industries (see Section 2.3). Cristobalite and tridymite are found in rocks and soil and are produced in some industrial operations when alpha quartz or amorphous silica is heated (such as foundry processes, calcining of diatomaceous earth, brick and ceramics manufacturing, and silicon carbide production) [NIOSH 1974; Weill et al. 1994; Virta 1993; Altieri et al. 1984]. Burning of agricultural waste or products such as rice hulls may also cause amorphous silica to become cristobalite (a crystalline form) [Rabovsky 1995; IARC 1997]. The other polymorphs (i.e., keatite, coesite, stishovite, and moganite) are rarely or never observed in nature [Ampian and Virta 1992].

1.2 Current Health Issues

Occupational exposure to respirable crystalline silica is a serious but preventable health hazard. Since 1968, reported mortality associated with silicosis has declined; however, 200 to 300 such deaths were reported each year during the period 1992–1995 [NIOSH 1996a; Althouse 1998]. Furthermore, the number of silicosis-related deaths among persons aged 15 to 44 did not decline substantially during 1968–1994, accounting for 207 of the 14,824 silicosis-related deaths during this period [CDC 1998a,b]. In addition, an unknown number of unreported or undiagnosed worker deaths occur each year from silicosis and other silica-related diseases such as pulmonary tuberculosis (TB), lung cancer, and scleroderma. The number of current cases of silicosis and silica-related disease in the United States is also unknown.

Prevention and elimination of silicosis and silica-related disease in the United States are priorities of the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), and the American Lung Association [DOL 1996]. International health agencies have also expressed concern about the continuing occurrence of silicosis and silica-related diseases. The International Agency for Research on Cancer (IARC) recently reviewed the results of post-1986 epidemiologic studies of lung cancer and occupational exposure to crystalline silica. They concluded that there is "sufficient evidence in

humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources" (i.e., IARC category "Group 1" carcinogen) [IARC 1997]. In 1991, the International Labour Office published a document describing methods for preventing and controlling occupational lung diseases, including silicosis [ILO 1991]. And in 1993, the Office of Occupational Health of the World Health Organization (WHO) called for increased medical surveillance of mineral-dust-exposed workers to prevent pneumoconioses such as silicosis and asbestosis [WHO 1993]. Epidemiologic studies published after the IARC review [IARC 1997] provide additional evidence for an exposure-response relationship of respirable crystalline silica with lung cancer mortality or morbidity (see Section 3.4.2.1).

Several recent epidemiologic studies indicate that current occupational standards are not sufficiently protective to prevent the occurrence of chronic silicosis. Epidemiologic studies of workers in the United States [Kreiss and Zhen 1996; Steenland and Brown 1995a; Rosenman et al. 1996; Hughes et al. 1998], Canada [Muir et al. 1989a,b; Muir 1991], Hong Kong [Ng and Chan 1994], and South Africa [Hnizdo and Sluis-Cremer 1993] have reported significant risks of silicosis over a working lifetime at concentrations of quartz or respirable dust containing quartz that are below the current NIOSH recommended exposure limit (REL) [NIOSH 1974], OSHA permissible exposure limit (PEL) [29 CFR*1910.1000], and the MSHA PEL [30 CFR 56, 57, 70, 71] (see Appendix and Table 12 in Chapter 3).

TB is an infectious disease that poses a threat to the health of silica-exposed workers and the public. A survey of U.S. mortality data for 1979 to 1991 reported that TB comortality was at least several times higher in decedents with silicosis than in decedents with asbestosis, with coal workers' pneumoconiosis (CWP), or without silicosis, asbestosis, or CWP [Althouse et al. 1995]. The U.S. Centers for Disease Control and Prevention (CDC), WHO, and the American Thoracic Society (ATS) have recently published information about risk factors for TB, including occupational exposure to respirable crystalline silica [CDC 1995; WHO 1996; ATS 1997]. The U.S. Environmental Protection Agency (EPA) suggested "further investigation" of the health effects of ambient crystalline silica exposures in potentially sensitive subgroups, including infants and persons with a respiratory infection or disease such as TB or pneumonia [EPA 1996].

Recent epidemiologic studies of occupational exposure to crystalline silica dust have also reported increased incidence of—or mortality from—extrapulmonary diseases such as scleroderma, rheumatoid arthritis, other autoimmune disorders, and renal disease [ATS 1997].

Experimental research has shown that crystalline silica is not an inert dust. The toxicity of crystalline silica particles is related to reactive sites on the surfaces of silica particles. Further discussion of in vitro studies of the biologic activity and factors that modify toxicity are found in Section 3.2.1 and Section 4.

1.3 History of NIOSH Activity

In 1974, NIOSH reviewed the available health effects data on occupational exposure to respirable crystalline silica and determined that the principal adverse health effect was silicosis [NIOSH 1974]. At that time, NIOSH recommended that occupational exposure to respirable crystalline silica dust be controlled so that workers would not be exposed to the airborne particulate at a time-weighted average (TWA)

Code of Federal Regulations. See CFR in references.

concentration greater than 50 micrograms per cubic meter of air (50 µg/m^3—or 0.05 mg/m^3), determined during a full-shift sample for up to a 10-hr workday during a 40-hr workweek. A later NIOSH report (*Review of the Literature on Crystalline Silica*) concluded that additional toxicologic and epidemiologic studies were needed to determine (1) the relationship between respirable crystalline silica dose and the risk of developing silicosis and lung cancer and (2) the adverse effects of crystalline silica on the kidney [NIOSH 1983a]. Since then, additional studies reported an increased incidence of malignant tumors in the lungs of rats exposed to either inhalation or intratracheal administration of various forms and preparations of respirable crystalline silica [Holland et al. 1986; Dagle et al. 1986; Groth et al. 1986; Muhle et al. 1989; Spiethoff et al. 1992]. On the basis of the evidence from the animal studies published by 1986, IARC concluded that "sufficient evidence" existed for the carcinogenicity of respirable crystalline silica in experimental animals but only "limited evidence" existed for carcinogenicity in humans [IARC 1987]. During the 1988 OSHA rulemaking activity on air contaminants, NIOSH recommended an exposure limit of 0.05 mg/m^3 "as respirable free silica for all crystalline forms of silica" to protect workers from silicosis and cancer [54 Fed. Reg.* 2521 (1989)]. In addition, NIOSH testimony referred to the IARC [1987] review and recommended that OSHA label crystalline silica a potential occupational carcinogen [54 Fed. Reg. 2521 (1989)].

1.4 Purpose and Scope

The numerous health effects of occupational exposure to respirable crystalline silica are reviewed in the chapters of several recent books [Graham 1998; Davis 1996; Green and Vallyathan 1996; McDonald 1996; Seaton 1995; Morgan and Reger 1995; Elmes 1994; Goldsmith 1994a,b; Weill et al. 1994; Wagner 1994]. This NIOSH Hazard Review summarizes the health effects of occupational exposure to respirable crystalline silica reported in literature published through March 1999. The review emphasizes recent important epidemiologic studies of occupational exposure to respirable crystalline silica with regard to (1) the quantitative risk of chronic silicosis, (2) lung cancer, (3) autoimmune disease, (4) chronic renal disease, and (5) chronic obstructive pulmonary disease. In addition, the review describes limitations of the current sampling and analytical methods for quantifying occupational exposures to silica.

Federal Register. See Fed. Reg. in references.

2 Properties, Production, and Potential for Exposure

2.1 Chemical and Physical Properties

In the crystalline state, one silicon atom and four oxygen atoms are arranged in an ordered, repetitive array of three-dimensional tetrahedrons. The silicon atom is the center of the tetrahedron. Each of the four corners consists of a shared oxygen atom.

Exposure to changes in temperature and pressure, either natural or synthetic, may cause the crystalline structure to change [Iler 1979; Klein and Hurlbut 1993; Navrotsky 1994; Hemley et al. 1994; IARC 1997]. An example of a naturally occurring pressure change is the transformation of alpha quartz to coesite in a rock subjected to the impact of a large meteorite [Iler 1979; Klein and Hurlbut 1993; IARC 1997]. Alpha quartz and beta quartz are the respective designations given to the low- and high-temperature crystal structures. Quartz changes from the alpha to the beta form at 573 °C (1,063 °F) [Ampian and Virta 1992; NIOSH 1983a; Virta 1993; Guthrie and Heaney 1995].

The solubility of quartz in water at room temperature ranges from 6 to 11 micrograms per cubic centimeter ($\mu g/cm^3$) (6 to 11 parts per million [ppm]) as SiO_2 [Coyle 1982; Iler 1979]. Quartz is slightly soluble in body fluids, where it forms silicic acid and is excreted by the urinary system [IARC 1987]. The amount of silica dissolved depends on various factors, including particle size, shape, and structure; solution temperature; viscosity; pH; the proportion of dust to liquid; and the presence of trace minerals [King and McGeorge 1938; King 1937; Iler 1979; Wiecek 1988; IARC 1997; Guthrie 1997]. However, the dissolution of quartz does not contribute substantially to its clearance or to changes in its biological activity [IARC 1997; Heppleston 1984; Vigliani and Pernis 1958].

2.2 Number of Workers Potentially Exposed

NIOSH [1991] estimates that at least 1.7 million U.S. workers are potentially exposed to respirable crystalline silica. This estimate is based on information from the National Occupational Exposure Survey (NOES) [NIOSH 1983b] and the *County Business Patterns 1986* [Bureau of the Census 1986]. Table 1 lists the nonmining industries (excluding agriculture) and mining industries with the largest numbers of workers potentially exposed to respirable crystalline silica. In addition, an undetermined portion of the 3.7 million U.S. agricultural workers [Bureau of the Census 1997] may be exposed to dust containing a significant percentage of respirable crystalline silica [Linch et al. 1998].

2.3 Dust-Generating Activities, Uses, and Potential Exposures

Crystalline silica (quartz) is a component of nearly every mineral deposit [Greskevitch et al. 1992]. Thus most crystalline silica exposures are to mixed dust with variable silica content that must be measured by dust collection and

Table 1. Nonmining and mining industries with the largest numbers of U.S. workers potentially exposed to respirable crystalline silica, 1986

SIC*	Industry	Estimated number of workers potentially exposed (1986)†	% total workers exposed (NOES)
Nonmining industries:			
174	Masonry, stonework, tile setting, and plastering	131,986	32.7
734	Services to dwellings and other buildings	65,812	10.3
327	Concrete, gypsum, and plaster products	63,456	33.3
176	Roofing and sheet metal work	51,153	25.3
356	General industrial machinery and equipment	44,991	16.2
807	Medical and dental laboratories	37,063	30.0
493	Combination of gas and electric and other utilities	35,074	21.2
179	Miscellaneous special trade contractors	32,615	7.8
753	Automotive repair shops	30,826	7.1
326	Pottery and related products	29,772	81.7
Mining industries:			
13	Oil and gas extraction	408,175	100‡
12	Bituminous coal and lignite mining	174,131	100
14	Mining and quarrying of nonmetallic minerals, except fuels	100,546	100
10	Metal mining	39,856	100

Source: NIOSH [1991].
*Standard industrial classification.
†Estimated number of workers potentially exposed to the hazards of flint, quartz, sand, or silica powder; based on data from the *County Business Patterns 1986* [Bureau of the Census 1986] and the National Occupational Exposure Survey (NOES) [NIOSH 1983b]. For SICs in which the estimates differed for individual hazards, the highest percentage was used for that SIC.
‡Exposure is assumed to be 100% in the mining industries.

analysis [Wagner 1995; Donaldson and Borm 1998].

Workers in a large variety of industries and occupations may be exposed to crystalline silica because of its widespread natural occurrence and the wide uses of the materials and products containing it. OSHA compliance officers found respirable quartz in 6,779 personal samples (8-hr TWA) taken in 255 industries that were targeted for inspection (excluding mining and agriculture). In 48% of the industries, average overall exposure exceeded the PEL for respirable quartz [Freeman and Grossman 1995]. Linch et al. [1998] applied an algorithm to OSHA compliance data from the period 1979–1995 and *County Business Patterns 1993* data [Bureau of the Census 1993] to estimate the percentage of workers by industry (excluding mining and agriculture) exposed to defined concentrations of respirable crystalline silica (e.g., ≥0.05 mg/m^3) in 1993. Area samples and samples involving complaints to OSHA were excluded from the analysis. Although data limitations could have resulted in underestimating or overestimating the number of workers exposed, the authors found 5 three-digit standardized industrial classification (SIC) codes in which an estimated number of workers were exposed to concentrations at least 10 times the NIOSH REL:

SIC		*No. workers*
174	Masonry and plastering	13,800 (1.8%)
162	Heavy construction	6,300 (1.3%)
172	Painting and paper hanging	3,000 (1.9%)
332	Iron and steel foundries	800 (0.3%)
347	Metal services	400 (0.2%)

Additional three-digit SICs had a number of workers with crystalline silica exposures that were two or five times higher than the NIOSH REL [Linch et al. 1998].

Table 2 lists the main industries around the world in which silica exposure has been reported. Virtually any process that involves movement of earth or disturbance of silica-containing products such as masonry and concrete may expose a worker to silica (see Table 3 for uses of industrial silica sand and gravel). Table 4 presents, from selected States, the most frequently recorded occupations of U.S. residents aged 15 or above whose death certificates list silicosis as an underlying or contributory cause of death [NIOSH 1996a]. In addition, Table 5 lists published case reports of silicosis in workers from other industries and occupations.

2.4 Sampling and Analytical Methods

Historically, several methods have been used to measure worker exposure to airborne crystalline silica (quartz, cristobalite, or tridymite). These methods differ primarily in the analytical technique employed, although they all rely on a collection procedure that uses a cyclone for size-selective sampling. Airborne samples are collected using a cyclone to remove nonrespirable particles and an appropriate filter medium (e.g., polyvinyl chloride) to retain the respirable dust fraction. Preparation of the sample for crystalline silica determination differs depending on the type of analytical technique used. One of three analytical techniques is typically used for the quantitative determination of crystalline silica: X-ray diffraction (XRD) spectrometry, infrared absorption (IR) spectrometry, or colorimetric spectrophotometry. XRD and IR are the most common techniques used for crystalline silica analyses. The quantitative limit of detection for these methods ranges from 5 to 10 µg per sample; but the accuracy is poor, particularly at the low filter loadings (≤30 µg per sample) that are typically collected when workplace concentrations of airborne crystalline silica are near the NIOSH REL of 50 µg/m^3 (or 0.05 mg/m^3).

Table 2. Main industries and activities around the world in which silica exposure has been reported

Industry or activity	Operations and tasks	Source materials
Agriculture	Plowing, harvesting, using machinery, burning agricultural waste, processing agricultural products	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and nonmetal, coal), rock drilling, dredging	Ores, associated rock
Quarrying and related milling operations	Crushing stone, sand and gravel processing, stone monument cutting and abrasive blasting, slate work (e.g., pencil manufacturing), diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures and buildings, highway and tunnel construction, excavation and earth moving and digging, masonry, concrete work, demolition, dry sweeping and brushing, pressurized air blowing, jack hammering, laying railroad track, removing rust or paint, sanding and scaling, replacement of asphalt roofing, and hauling, pouring, mixing, or dumping silica-containing materials	Sand, concrete, rock, soil, mortar, plaster, shingles
Glass, including fiberglass	Raw material processing, refractory installation and repair	Sand, crushed quartz, refractory materials
Cement	Raw material processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production, abrasive products fabrication	Sand, tripoli, sandstone
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, molding, glaze or enamel spraying, finishing, sculpting, firing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material

(Continued)

Sources: IARC [1987; 1997], NIOSH [1979a; 1983a,b; 1996b], DOL, NIOSH [1997], Fulekar and Alam Khan [1995], Jain et al. [1977], Corn [1980], Webster [1982], Froines et al. [1986], Davis [1996], Weill et al. [1994], Lucas and Salisbury [1992], Pike [1992], McCunney et al. [1987], Fairfax [1998].

Table 2 (Continued). Main industries and activities around the world in which silica exposure has been reported

Industry or activity	Operations and tasks	Source materials
Silicon and ferro-silicon foundries (ferrous and nonferrous)	Raw materials handling, casting, molding and shaking out, abrasive blasting, fettling, furnace installation and repair	Sand, refractory material
Metal products, including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand
Rubber and plastics	Raw materials handling	Fillers (tripoli, diatomaceous earth)
Paint	Raw materials handling, site preparation	Fillers (tripoli, diatomaceous earth, silica flour)
Soaps and cosmetics	Manufacturing or occupational use of abrasive soaps and scouring powders	Silica flour
Roofing asphalt felt	Filling and granule application	Sand and aggregate, diatomaceous earth
Agricultural chemicals	Raw material crushing, handling, bagging; or dumping products or raw materials	Phosphate ores and rock
Jewelry	Cutting, grinding, polishing, buffing, etching, engraving, casting, chipping, sharpening, sculpting	Semiprecious gems or stones, abrasives, glass
Arts, crafts, sculpture	Pottery firing, ceramics, clay mixing, kiln repairs, abrasive blasting, sand blasting, engraving, cutting, grinding, polishing, buffing, etching, engraving, casting, chipping, sharpening, sculpting	Clays, glazes, bricks, stones, rocks, minerals, sand, silica flour
Dental material	Sand blasting, polishing	Sand, abrasives
Boiler scaling	Coal-fired boilers	Ash and concretions
Automobile repair	Abrasive blasting, sanding, removing paint and rust	Sand, metals, priming putty

Table 3. Industrial silica sand and gravel sold or used by U.S. producers in 1994, by major end use

General use	End use
Sand:	
Glass-making	Containers, flat (plate and window), specialty, fiberglass (unground or ground)
Foundry work	Molding and core, molding and core facing (ground), refractory
Metallurgical work	Silicon carbide, flux for metal smelting
Abrasive work	Blasting, scouring cleansers (ground), sawing and sanding, chemicals (ground and unground)
Fillers	Rubber, paints, putty, whole grain fillers/building products
Ceramics	Pottery, brick, tile
Filtration	Water (municipal, county, local), swimming pool, others
Petroleum manufacturing	Hydraulic fracturing, well packing, and cementing
Recreation	Golf course, baseball, volleyball, play sands, beaches, traction (engine), roofing granules and fillers, other (ground silica or whole grain)
Gravel	Silicon, ferrosilicon, filtration, nonmetallurgical flux, other

Sources: IARC [1997]; BOM [1994].

Table 4. Most frequently recorded occupations of U.S. residents aged 15 or above whose death certificates list silicosis as an underlying or contributory cause of death—selected States, 1991–1992[*]

COC[†]	Occupation	Number	%
616	Mining machine operator	39	16.0
889	Laborer, except construction	29	11.9
019	Manager or administrator, not elsewhere classified	11	4.5
633	Supervisor or precision production occupations	11	4.5
453	Janitor, cleaner	8	3.3
719	Molding, casting machine operator	8	3.3
243	Supervisor or proprietor of sales occupations	6	2.5
844	Operating engineer	6	2.5
637	Machinist	5	2.1
787	Hand molding, casting, and forming occupations	5	2.1
—	All other occupations	109	44.9
—	Occupation not reported	6	2.5
	TOTAL	243	100.1[‡]

Source: NIOSH [1996a].
[*]Data for 1985–1990 are reported in Table 4–11 of NIOSH [1994d].
[†]COC: 1980 census occupation code.
[‡] Column does not add to 100.0 because of rounding.

Table 5. Other occupations* reporting cases of silicosis in workers

Industry or occupation	Reference
Agriculture industry or forestry worker	Fennerty et al. [1983]; Dynnik et al. [1981]; Beaumont et al. [1995]
Brewery worker	Nemery et al. [1993]
Confectioner	Canessa et al. [1990]
Crystal cutter	Suskovic et al. [1990]
Drycleaning worker	Seitz et al. [1982]
Filter candle production worker	Vigliani and Mottura [1948]
Grave digger and well digger	al-Kassimi et al. [1991]
Kaolin worker	Rodriguez et al. [1985]
Metal polisher	Malik et al. [1985]
Pit digger	de Barros Hatem and Cavalcanti [1990]
Souvenir casting worker	Carel et al. [1994]
Woodworker	Thoreux et al. [1990]

*Includes only occupations not listed in Tables 2 or 4.

2.4.1 Sampling Methods

Current sampling methods for crystalline silica involve the use of a cyclone attached to a filter cassette to collect the respirable fraction of the airborne particulate. To minimize measurement bias and variability, these samplers should conform to the criteria of the International Organization for Standardization (ISO), the European Standardization Committee (CEN), and the American Conference of Governmental Industrial Hygienists (ACGIH) for collecting particles of the appropriate size [ISO 1991; CEN 1992; ACGIH 2001]. Also, the cyclone should exhibit sufficient conductivity to minimize the electrostatic effects on particle collection. Cyclones typically used for crystalline silica measurements include the Dorr-Oliver 10-mm nylon cyclone and the Higgins-Dewell conductive cyclone. These cyclones have been evaluated for their compliance with the ISO/CEN/ACGIH respirable aerosol sampling convention. Flow rates of 1.7 L/min for the Dorr-Oliver cyclone and 2.2 L/min for the Higgins-Dewell cyclone provide minimum bias for a wide range of particle size distributions that are likely to occur in the workplace [Bartley et al. 1994]. The Dorr-Oliver 10-mm cyclone is required by MSHA, and the Higgins-Dewell cyclone is used in the United Kingdom. Recently, the GK2.69 cyclone [Kenny and Gussman 1997] has become available with a sampling rate equal to 4.2 L/min. The GK2.69 cyclone is expected to be at least as adequate as the nylon cyclone for conforming to the ISO/CEN/ACGIH respirable aerosol sampling convention; and it may be preferable for silica sampling since it is conductive, has well-defined dimensional characteristics, and can be used at higher flow rates for better mass sensitivity. Because each type of cyclone exhibits specific particle collection characteristics, the use of a single cyclone type for each application would be advisable until evidence becomes available indicating that bias among cyclone types will not increase laboratory-to-laboratory variability.

Cyclones and filter cassettes should be leak tested to avoid gross failure in the field. The cyclones may be tested using a simple pressure- (or vacuum-) holding test. The filter cassette should also be checked for leakage while attached to the cyclone. Two approaches to testing the cassettes have been used. A micromanometer has been used to measure the pressure drop across a single type of cassette and compare it with the average pressure drop across well-sealed cassettes [Van den Heever 1994]. An alternative approach uses a particle counter to measure the penetration of submicrometer ambient aerosol through the cassette, with the percentage of penetration serving as an indicator of leakage [Baron 2001]. Measurement of cassette leakage by several laboratories indicates that significant leakage can occur in certain situations. Cassettes should be assembled using a press, and they should be routinely checked for leakage.

2.4.2 Analytical Methods

2.4.2.1 XRD Spectrometry

XRD methods used for crystalline silica determination include NIOSH Method 7500 [NIOSH 1998], OSHA Method ID–142 [OSHA 1996], MSHA Method P–2 [MSHA 1999], and the Health and Safety Executive (HSE) Method for the Determination of Hazardous Substances (MDHS) 51/2 [HSE 1988]. Details of these methods are presented in Table 6. XRD is capable of distinguishing the three prevalent polymorphs of crystalline silica (quartz, cristobalite, and tridymite) and can simultaneously analyze for each polymorph while correcting for interferences that may be present on the sample [Madsen et al. 1995]. Although most samples collected in industrial workplaces are relatively free of mineral interferences, an XRD scan of some samples should be performed to ensure the absence of interferences through confirmation of the correct peak ratios for the three largest peaks.

Table 6. XRD* sampling and analytical methods for crystalline silica

Item	NIOSH Method 7500	OSHA Method ID-142	MSHA Method P-2	MDHS 51/2
Silica polymorph	Quartz, cristobalite, tridymite	Quartz, cristobalite	Quartz, cristobalite	Quartz
Sampler	10-mm nylon cyclone, 1.7 L/min; Higgins-Dewell cyclone, 2.2 L/min	10-mm nylon Dorr-Oliver cyclone, 1.7 L/min	10-mm nylon Dorr-Oliver cyclone, 1.7 L/min	Higgins-Dewell cyclone, 1.9 L/min
Filter	37-mm, 5-µm PVC membrane	37-mm, 5-µm PVC membrane	37-mm, 5-µm PVC membrane	25-mm, 5-µm PVC membrane
Volume	400–1,000 L; total dust < 2 mg	408–816 L; total dust < 3 mg	400–1,000 L; total dust < 3 mg	≥456 L; total dust < 2 mg
Filter preparation	RF plasma asher, muffle furnace, or filter dissolution in THF	Dissolve filter in THF	RF plasma asher	None
Redeposition	On 0.45-µm silver membrane filter	On 0.45-µm silver membrane filter	On 0.45-µm silver membrane filter	None
Drift correction	Silver internal standard	Silver internal standard	Silver internal standard	External standard (e.g., aluminum plate)
X-ray source	Cu K_α; 40 kV, 35 mA	Cu K_α; 40 kV, 40 mA	Cu K_α; 55 kV, 40 mA	Cu K_α; 45 kV, 45 mA
Calibration	Suspensions of SiO_2 in 2-propanol (deposited on silver membrane filter)	Suspensions of SiO_2 in 2-propanol (deposited on silver membrane filter)	Suspensions of SiO_2 in 2-propanol (deposited on silver membrane filter)	Sampling from a generated atmosphere of standard quartz dust
Proficiency testing	PAT	PAT	PAT	WASP
Range (µg quartz)	20–2000	50–160 (validation range)	20–500	50–2000
LOD (µg quartz)	5 (estimated)	10	5	3
Precision	$\overline{RSD}$ = 0.08 50–200 µg	$\overline{CV}$ = 0.106 @ 50–160 µg	CV = 10 % @ 20–500 µg	CV = 5 % @ 50 µg

*Abbreviations: Cu = copper; CV = coefficient of variation (equivalent to RSD); $\overline{cv}$ = pooled coefficient of variation; K_α = electron ionization energy; kV = kilovolt(s); LOD = limit of detection; mA = milliampere(s); MDHS = Methods for the Determination of Hazardous Substances (Health and Safety Executive, United Kingdom); MSHA = Mine Safety and Health Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PAT = proficiency analytical testing; PVC = polyvinyl chloride; RF = radio frequency; RSD = relative standard deviation; $\overline{RSD}$ = pooled relative standard deviation (equivalent to $\overline{cv}$); THF = tetrahydrofuran; WASP = Workplace Analysis Scheme for Proficiency; XRD = X-ray diffraction.

2.4.2.2 IR Spectrometry

IR methods used for crystalline silica determination include NIOSH Methods 7602 and 7603 [NIOSH 1994a,c], MSHA Method P–7 [MSHA 1994], and MDHS 37 and 38 [HSE 1987, 1984]. Details of these methods are presented in Table 7. Although IR is less specific than XRD (IR methods cannot readily distinguish crystalline silica polymorphs), the technique is less expensive and can be optimized for measuring quartz in well-defined sample matrices [Madsen et al. 1995; Smith 1997; Hurst et al. 1997]. Samples that contain other silicates (such as kaolinite) and amorphous silica can present interferences in the analyses. Also, a potential for bias exists when correcting for matrix absorption effects, with an increasing risk of bias at lower quartz concentrations.

2.4.2.3 Colorimetric Spectrophotometry

The NIOSH colorimetric method for crystalline silica (NIOSH Method 7601) [NIOSH 1994b] is significantly less precise than IR or XRD methods. The colorimetric analytical method exhibits a nonlinear dependence on the mass of crystalline silica present [Eller et al. 1999a]. The linear range of the method is limited, and the blank values for samples can be high (20 µg silica or higher) [Talvitie 1951, 1964; Talvitie and Hyslop 1958]. High intralaboratory variability of the method (up to twice that of IR or XRD) has been noted in studies conducted in the Proficiency Analytical Testing Program (PAT) [Shulman et al. 1992]. The colorimetric method cannot distinguish between silica and silicates, since it is based on the measurement of silicon.

2.4.2.4 Factors Affecting the Sensitivity and Accuracy of Analytical Techniques

Samples prepared for XRD analyses are measured directly (MDHS 51/2) or are redeposited onto 25-mm silver membrane filters (NIOSH Method 7500 and OSHA Method ID–142). IR samples can be measured directly (MDHS 37), redeposited on an acrylic copolymer membrane filter (NIOSH Method 7603 and MSHA Method P–7), or incorporated into a potassium bromide (KBr) pellet (NIOSH Method 7602 and MDHS 38). Techniques used for redepositing the sample (both IR and XRD) are difficult to perform at low sample loadings and require the laboratory analyst to demonstrate good intralaboratory reproducibility. However, these techniques can be optimized by preparing multiple working standards from multiple suspensions of calibration standards and by ensuring that the sample is redeposited evenly as a thin layer on the filter. No statistically significant difference has been observed between ashing the filter (muffle furnace and low-temperature asher) and dissolving the filter by tetrahydrofuran before redepositing the sample [Eller et al. 1999a].

The instrument response of all three analytical techniques is influenced by the size of the particles in the sample. With XRD, the diffraction intensity (as measured by peak height) can vary considerably with particle size, with smaller particles showing lower intensities [Bhaskar et al. 1994]. The sensitivity of IR analyses decreases with increasing particle size. The colorimetric method requires the use of a precisely timed heating step with phosphoric acid to digest amorphous silica and silicates during sample preparation, causing a possible loss of some small crystalline silica particles [Eller et al. 1999a]. Since particle size affects the sensitivity of all three analytical techniques, the particle size distribution of the calibration standard should closely match the size of the particles retained on the collected sample.

For all analytical techniques, strict adherence to standardized procedures is necessary to produce accurate results. Specifically, appropriate

Table 7. IR* sampling and analytical methods for crystalline silica

Item	NIOSH Method 7602	NIOSH Method 7603	MSHA P–7	MDHS 37	MDHS 38
Matrix		Coal mine dust	Coal mine dust		
Sampler	10-mm nylon cyclone, 1.7 L/min; Higgins-Dewell cyclone, 2.2 L/min	10-mm nylon cyclone, 1.7 L/min; Higgins-Dewell cyclone, 2.2 L/min	10-mm nylon Dorr-Oliver cyclone, 2.0 L/min	Higgins-Dewell cyclone, 1.9 L/min	Higgins-Dewell cyclone, 1.9 L/min
Filter	37-mm filter; 5-µm PVC or MCE membrane	37-mm filter; 5-µm PVC membrane	37-mm filter; 5-µm PVC membrane, preweighed	37-mm filter; 5-µm PVC membrane	37-mm filter; 5-µm PVC membrane
Volume	400–800 L; total dust <2 mg	300–1,000 L; total dust <2 mg	Not stated	≥456 L; total dust <1 mg	≥456 L; total dust <0.7mg
Filter preparation	RF plasma asher or muffle furnace	RF plasma asher or muffle furnace	RF plasma asher	None	Muffle furnace
Analytical sample preparation	Mix residue with KBr, press 13-mm pellet	Redeposit on 0.45-µm acrylic copolymer filter	Redeposit on 0.45-µm acrylic copolymer filter	None	Mix residue with KBr, press 13-mm pellet
Standard	Polystyrene film	Polystyrene film	Polystyrene film	Polystyrene film	Polystyrene film
Calibration	Quartz diluted in KBr	Standard suspension of quartz in 2-propanol	Standard suspension of quartz in 2-propanol	Sampling from a generated atmosphere of standard quartz dust	Sampling from a generated atmosphere of standard quartz dust
Proficiency testing	PAT	PAT	PAT	WASP	WASP
Range (µg quartz)	10–160	30–250	25–250	10–1,000	5–700
LOD (µg quartz)	5 (estimated)	10 (estimated)	10	Varies with particle size	Varies with particle size

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See footnote at end of table.

(Continued)

Table 7 (Continued). IR* sampling and analytical methods for crystalline silica

Item	NIOSH Method 7602	NIOSH Method 7603	MSHA P–7	MDHS 37	MDHS 38
Precision	$\overline{RSD}$ <0.15 @ 30µg	$\overline{RSD}$ = 0.098 @ 100–500µg	CV = 5–10 % @ 100–500 µg	CV = 5 % @ 50 µg	CV = 5 % @ 50 µg

*Abbreviations: CV = coefficient of variation (equivalent to RSD, relative standard deviation); IR = infrared absorption; KBr = potassium bromide; MCE = methyl cellulose ester; MDHS = Methods for the Determination of Hazardous Substances (Health and Safety Executive, United Kingdom); MSHA = Mine Safety and Health Administration; NIOSH = National Institute for Occupational Safety and Health; LOD = limit of detection; PAT = proficiency analytical testing; PVC = polyvinyl chloride; RF = radio frequency; $\overline{RSD}$ = pooled relative standard deviation (equivalent to $\overline{CV}$,pooled coefficient of variation); WASP = Workplace Analysis Scheme for Proficiency.

calibration of the technique has been shown to be critical in the accurate measurement of crystalline silica [Eller et al. 1999b]. Also, it is essential that only standard reference materials from the National Institute of Standards and Technology (NIST) (for which particle size and phase purity has been established) be used to prepare calibration curves for quartz (1878a) and cristobalite (1879a) [Eller et al. 1999a]. No standard reference material for tridymite is available, since this silica polymorph rarely exists in the workplace. However, a well-characterized sample of tridymite of the appropriate particle size is available from the U.S. Geological Survey* and can be used as a reference standard.

Direct-on-filter techniques are used by the United Kingdom, the European Union, and Australia [Madsen et al. 1995]. These techniques require less time and labor than others and are amenable to both XRD and IR analyses [Lorberau et al. 1990]. However, direct-on-filter techniques are affected by the manner in which the particles are deposited on the filter sample (particle deposition may be nonuniform). Thus care must be taken when choosing the area of the filter to measure so that results can be compared with other methods. Sample overloading is possible for a sample collected over a full work shift.

2.4.3 Feasibility of Measuring Crystalline Silica at Various Concentrations

The efficacy of sampling and analytical methods for measuring concentrations of hazardous materials may be established using the NIOSH accuracy criterion [NIOSH 1995b], which requires better than 25% accuracy at concentrations of expected method application. Accuracy, as a percentage of true concentration values, is defined in terms of an interval expected to contain 95% of (future) measurements. To account for uncertainty in method evaluations, the upper 95% confidence limit on the accuracy is measured and used in the criterion. Generally, the accuracy of a method is measured over a range of concentrations bracketing the OSHA PEL. Use of a range of measurements means that accuracy is assured—both at concentrations below the PEL (for possible use in action level determinations) and, more significantly, at the PEL (where method results must be legally defensible).

NIOSH has evaluated both the XRD silica method (NIOSH Method P&CAM 259, the forerunner to NIOSH Method 7500) [NIOSH 1979b] and an IR silica method (MSHA Method P–7, equivalent to NIOSH Method 7603) in a collaborative test among several laboratories [NIOSH, BOM 1983]. One result of the test was that the accuracy of the methods was estimated by evaluating the intralaboratory variability at various filter loadings. The concentrations to which these filter loadings correspond depend on the flow rate of the presampler used. Experimental conditions and results relevant to the derivation of these estimates are summarized in Tables 8 and 9. The results of the collaborative tests indicate that both the XRD and IR methods tested meet the NIOSH accuracy criterion [NIOSH 1995b] over the range of filter loadings measured. Currently, OSHA uses the 10-mm nylon cyclone at a sampling rate of 1.7 L/min for sampling crystalline silica. The concentrations relevant to the collaborative test conditions are listed in Tables 10 and 11 and assume an 8-hr sampling period. As indicated in Tables 10 and 11, the traditional nylon cyclone meets the

*Tridymite reference material may be obtained from Dr. Stephen A. Wilson, U.S. Geological Survey, Box 25046, MS 973, Denver, CO 80225 (telephone: 303–236–2454; FAX: 303–236–3200; e-mail: swilson@usgs.gov; Web site: http://minerals.cr.usgs.gov/geochem).

Table 8. Intralaboratory results for evaluation of XRD silica method

Item	Filter loading		
	69.4 μg	98.4 μg	204 μg
Degrees of freedom	12	11	12
RSD for sampling and analytical methods (%)[*,†]	8.8	6.3	8.1

Source: NIOSH, BOM [1983].
[*]RSD = relative standard deviation. RSD for sampling and analytical methods represents the RSD in mass estimates, accounting for intersampler and analytical variability.
[†]Implications for XRD: Pooled filter levels and pump error (assumed to be <5%) indicate that the overall imprecision is as follows: Total RSD for sampling and analytical methods is 9.3%. Therefore, the upper 95% confidence limit on the accuracy (35 degrees of freedom) is 21%.

Table 9. Intralaboratory results for evaluation of IR silica method

Item	Filter loading		
	67.2 μg	99.7μg	161 μg
Degrees of freedom	10	12	11
RSD for sampling and analytical methods (%)[*,†]	5.8	7.8	7.4

Source: NIOSH, BOM [1983].
[*]RSD = relative standard deviation. RSD for sampling and analytical methods represents the RSD in mass estimates, accounting for intersampler and analytical variability.
[†]Implications for IR: Pooled filter levels and pump error (assumed to be <5%) indicate that the overall imprecision is as follows: Total RSD for sampling and analytical methods is 7.1%. Therefore, the upper 95% confidence limit on the accuracy (33 degrees of freedom) is 17%.

Table 10. XRD method evaluation: concentration ranges bracketing applicable exposure limits for which the NIOSH accuracy criterion is met* ($\mu g/m^3$)

Cyclone and sampling rate	Filter loading			Applicable exposure limit
	69.4 μg	98.4 μg	204 μg	
Nylon cyclone, 1.7 L/min	85	121	251	100
GK2.69 cyclone, 4.2 L/min	34	49	102	50

*Eight-hour sampled masses are combined with results of NIOSH, BOM [1983].

Table 11. IR method: concentration ranges bracketing applicable exposure limits for which the NIOSH accuracy criterion is met* ($\mu g/m^3$)

Cyclone and sampling rate	Filter loading			Applicable exposure limit
	6.72 μg	99.7 μg	161 μg	
Nylon cyclone, 1.7 L/min	83	123	198	100
GK2.69 cyclone, 4.2 L/min	34	50	80	50

*Eight-hour sampled masses are combined with results of NIOSH, BOM [1983].

accuracy criterion over a range of concentrations bracketing 100 μg/m^3.

Since the GK2.69 cyclone is expected to conform to the ISO/CEN/ACGIH respirable aerosol sampling convention, the NIOSH intralaboratory collaborative tests can be used to establish confidence limits on its accuracy. The results of the collaborative tests indicate that the GK2.69 cyclone meets the accuracy criterion over a range of concentrations bracketing 50 μg/m^3, as illustrated in Tables 10 and 11.

3 Human Health Effects

3.1 Epidemiologic Considerations in Occupational Respiratory Disease Studies

3.1.1 Study Designs

Epidemiology is the study of patterns of disease occurrence in human populations and the factors that influence those patterns [Lilienfeld and Stolley 1994]. Epidemiology is the primary science used to study silica-related diseases in workers. Most epidemiologic studies of silica-exposed workers discussed in this review are cross-sectional studies (i.e., prevalence studies) or retrospective (i.e., historical) cohort studies. Cross-sectional studies measure symptom or disease occurrence in a selected population at one point in time. An example of a cross-sectional study design would be the spirometric testing of lung function in a group of granite shed workers during an annual health survey and comparison with respiratory function in nongranite workers. Cross-sectional studies have two disadvantages:

- Usually only the "survivor" population is examined. Retired, former, or deceased workers are not included, possibly resulting in an underestimate of the disease prevalence.
- It may be impossible to determine whether exposure preceded the disease if both are measured at the same time.

Many epidemiologic studies of silica-related diseases are retrospective cohort morbidity or mortality studies. In this approach, the illnesses, deaths, and exposures (surrogate or reconstructed) of an entire cohort (e.g., all workers ever employed in one foundry) are followed forward from a time in the past to a

Photograph by Kenneth Linch, NIOSH

Construction workers drilling holes in concrete pavement during highway repair.

designated time in the future, and the number and causes of deaths that occur in that interval are assessed. Exposures for the followup period may be reconstructed from historical information or a surrogate measure such as duration of employment. The mortality of the cohort is then compared with the mortality of a standard population. For example, Steenland and Brown [1995b] used a retrospective study design to examine the mortality of a cohort of white male underground gold miners employed for at least 1 year between 1940 and 1965. The miners were followed from their first date of mining employment to their date of death or until the end of 1990, whichever came first. Their mortality was then compared with that of the U.S. population or the county where the mine was located. A disadvantage of silicosis mortality studies that use death certificate data is that silicosis cases could be underascertained even when contributing causes of death are included, as suggested by a study of silicosis mortality surveillance in the United States [Bang et al. 1995].

3.1.2 Sources of Bias

Three main (but not mutually exclusive) types of bias may affect the results of epidemiologic studies of silica-exposed workers—selection bias, information bias, and confounding [Checkoway 1995]:

- ***Selection bias*** originates from the method of choosing study subjects. This type of bias is a common criticism of lung cancer studies of compensated silicotics because silicotic workers who sought compensation for their disease may differ from all silicotics in symptoms, radiographic changes, social and psychological factors, and industry [Weill and McDonald 1996; McDonald 1995]. However, Goldsmith [1998] reviewed this question and concluded that lung cancer risk estimates were not higher in compensated silicotics when compared with those of silicotics ascertained from other clinical sources (i.e., hospital or registry data).

- ***Information bias*** involves misclassification of study subjects by disease or exposure status [Checkoway et al. 1989]. An example of disease (silicosis) misclassification occurred in a study of North Carolina dusty trades workers [Amandus et al. 1991; Rice et al. 1986]: a re-evaluation of the chest X-rays found that 104 of the 370 cases categorized as silicosis were actually International Labour Organization (ILO) category 0 (nonsilicotic) [Amandus et al. 1992]. Sources of exposure assessment errors include instrument error, incorrect imputation of exposure when data are missing, and data extrapolation errors [Checkoway 1995]. Misclassification of exposure may occur in retrospective cohort studies of silicosis when quantitative dust exposure measurements are mathematically converted from particle counts to gravimetric respirable silica equivalents.

- ***Confounding variables*** are factors that are related to exposure and are also independent risk factors for the disease under study [Checkoway 1995]. Most studies of silica-related diseases controlled for confounding factors such as age and race by study design or data analysis. Confounding from cigarette smoking is an important concern in studies of lung cancer, bronchitis, asthma, emphysema, chronic obstructive pulmonary disease (COPD), and lung function. Confounding of an exposure-disease relationship by cigarette smoking is less likely when an internal comparison group is used—e.g., when both groups are from the same plant [Siemiatycki et al. 1988].

(Some studies in this review used external comparison populations.) Most of the lung cancer studies among underground miners did not control for the effects of other carcinogens that may have been present, such as arsenic, radon progeny, and diesel exhaust (see Section 3.4.1).

The effects of bias discussed here can be minimized by applying epidemiologic methods. Description of appropriate methodology is available in epidemiology textbooks.

3.2 Silicosis

3.2.1 Definition

Silicosis most commonly occurs as a diffuse nodular pulmonary fibrosis. This lung disease (which is sometimes asymptomatic [NIOSH 1996b]) is caused by the inhalation and deposition of respirable crystalline silica particles (i.e., particles <10 µm in diameter) [Ziskind et al. 1976; IARC 1987]. According to a report from the U.S. Surgeon General [DHHS 1985], cigarette smoking has "no significant causal role" in the etiology of silicosis. Probably the most important factor in the development of silicosis is the "dose" of respirable silica-containing dust in the workplace setting—that is, the product of the concentration of dust containing respirable silica in workplace air and the percentage of respirable silica in the total dust. Other important factors are (1) the particle size, (2) the crystalline or noncrystalline nature of the silica, (3) the duration of the dust exposure, and (4) the varying time period from first exposure to diagnosis (from several months to more than 30 years) [Banks 1996; Kreiss and Zhen 1996; Hnizdo and Sluis-Cremer 1993; Hnizdo et al. 1993; Steenland and Brown 1995a; ATS 1997]. Experimental evidence supporting the influence of these factors has recently been reviewed [Mossman and Churg 1998; Heppleston 1994]. Many in vitro studies have been conducted to investigate the surface characteristics of crystalline silica particles and their influence on fibrogenic activity [Bolsaitis and Wallace 1996; Fubini 1997, 1998; Castranova et al. 1996; Donaldson and Borm 1998; Erdogdu and Hasirci 1998]. These researchers found that a number of features may be related to silica cytotoxicity. Further research is needed to associate the surface characteristics with occupational exposure situations and health effects [Donaldson and Borm 1998]. Such exposure situations may include work processes that produce freshly fractured silica surfaces [Bolsaitis and Wallace 1996; Vallyathan et al. 1995] or that involve quartz contaminated with trace elements such as iron [Castranova et al. 1997].

A worker may develop one of three types of silicosis, depending on the airborne concentration of respirable crystalline silica: (1) chronic silicosis, which usually occurs after 10 or more years of exposure at relatively low concentrations; (2) accelerated silicosis, which develops 5 to 10 years after the first exposure; or (3) acute silicosis, which develops after exposure to high concentrations of respirable crystalline silica and results in symptoms within a period ranging from a few weeks to 5 years after the initial exposure [NIOSH 1996b; Parker and Wagner 1998; Ziskind et al. 1976; Peters 1986]. The symptoms of accelerated silicosis are similar to those of chronic silicosis, but clinical and radiographic progression is rapid. Also, fibrosis may be irregular and more diffuse [Banks 1996; Seaton 1995; Silicosis and Silicate Disease Committee 1988] or not apparent on the chest radiograph [Abraham and Weisenfeld 1997]. Acute silicosis is typically associated with a history of high exposures from tasks that produce small particles of airborne dust with a high silica content, such as sandblasting, rock drilling, or quartz milling [Davis 1996]. The pathologic characteristics of acute silicosis (sometimes referred to as silicoproteinosis) resemble those of alveolar proteinosis [Wagner 1994; Davis 1996].

Pulmonary fibrosis may not be present in acute silicosis [NIOSH 1996b].

Epidemiologic studies of gold miners in South Africa, granite quarry workers in Hong Kong, metal miners in Colorado, and coal miners in Scotland have shown that chronic silicosis may develop or progress even after occupational exposure to silica has been discontinued [Hessel et al. 1988; Hnizdo and Sluis-Cremer 1993; Hnizdo and Murray 1998; Ng et al. 1987; Kreiss and Zhen 1996; Miller et al. 1998]. Therefore, removing a worker from exposure after diagnosis does not guarantee that silicosis or silica-related disease will stop progressing or that an impaired worker's condition will stabilize [Parker and Wagner 1998; Weber and Banks 1994; Wagner 1994].

3.2.2 Epidemiologic Exposure-Response Models of Silicosis

This section reviews published epidemiologic studies that provide evidence of an exposure-response relationship for crystalline silica and silicosis using cumulative exposure data. Exposure-response models based on cumulative exposure data can predict silicosis risk for a particular silica dust exposure over a period of time. Epidemiologic studies that provided evidence of an exposure-response relationship for silica and silicosis on the basis of other kinds of exposure data (e.g., duration of exposure) have been reviewed elsewhere [EPA 1996; Davis 1996; Hughes 1995; Rice and Stayner 1995; Seaton 1995; Steenland and Brown 1995a; Goldsmith 1994a; WHO 1986].

Table 12 summarizes the published studies that predict the incidence or prevalence of radiographic silicosis based on models of cumulative exposure to respirable crystalline silica. Table 13 presents details about the cohorts, quartz content of the dust, followup periods, and limitations of each study. All of the studies predicted the occurrence of at least one case of radiographic silicosis per 100 workers at cumulative exposures approximately equal to the OSHA and MSHA PELs and the NIOSH REL over a 40- or 45-year working lifetime (see appendix for the PELs and REL). Three studies predicted prevalences of 47% to 95% at the OSHA PEL. Each study followed a cohort of miners for at least three decades from first employment in the industry [Kreiss and Zhen 1996; Hnizdo and Sluis-Cremer 1993; Steenland and Brown 1995a]. Studies of foundry workers [Rosenman et al. 1996], hardrock miners [Muir et al. 1989a,b; Muir 1991], and workers in the diatomaceous earth industry [Hughes et al. 1998] followed workers for less than 30 years (mean) and predicted prevalences of 1% to 3%. The studies presented in Table 12 predicted that approximately 1 to 7 silicosis cases per 100 workers would occur at respirable quartz concentrations of 0.025 mg/m^3—half the NIOSH REL of 0.05 mg/m^3—with the contingencies and exceptions noted in Table 12. However, that concentration cannot be measured accurately at this time for the reasons given in Section 2.4.

Table 12 does not include a cohort study of 1,416 coal miners exposed to coal dust with quartz concentrations ranging from 0.4% to 29.4% of respirable dust [Miller et al. 1998]. This study predicted pneumoconiosis risks for 47 men with a "profusion of median small opacities" of ILO category ≥2/1 (i.e., 2/1+), a higher category of radiographic abnormality than reported in the studies listed in Tables 12 and 13. Logistic regression models predicted that the risk of small opacities of 2/1+ at the time of followup examination would be about 5% for miners exposed to a mean respirable quartz concentration of 0.1 mg/m^3 and about 2% for miners exposed to a mean respirable quartz concentration of 0.05 mg/m^3 for about 15 years [Miller et al. 1998]. The predicted risks increased with cumulative exposure to respirable quartz dust.

Table 12. Predicted incidence or prevalence of silicosis following exposure to selected concentrations of respirable quartz dust—based on modeling of cumulative exposure over a 45-year working lifetime

Study and cohort	Selected mean concentration of respirable quartz dust (mg/m^3)	Mean time since first quartz exposure (yr)	Maximum time since first quartz exposure (yr)	Predicted incidence or prevalence of silicosis, ILO category ≥ 1/1 (cases/100 workers)
Hnizdo and Sluis-Cremer [1993], 2,235 South African gold miners	0.05	36[*]	50[*]	13[†]
	0.10	—	—	70[‡]
Hughes et al. [1998], 2,342 U.S. workers in a diatomaceous earth mining and processing facility	0.05	11.5	46	1.5[§]–4[‡,**]
	0.10	—	—	4[§]–17[‡,**]
Kreiss and Zhen [1996], 100 U.S. hardrock miners and 34 community controls	0.05	41.6[*]	66[*]	30[‡,††]
	0.10	33.5[‡‡]	68[‡‡]	90[‡,††]
Muir et al. [1989a,b] and Muir [1991], 2,109 Canadian gold and uranium miners	0.05	18	38[*]	0.09–0.62[§§]
Ng and Chan [1994], 338 Hong Kong granite workers	0.045[‡,***]	—[†††]	—[†††]	6
Rosenman et al. [1996], 1,072 U.S. gray iron foundry workers	0.05	28	>30	2[‡‡‡]
	0.10	—	—	3[‡‡‡]
Steenland and Brown [1995a], 3,330 U.S. gold miners	0.05	37	73[§§§]	10[****]
	0.09	—	—	47[****]

[*]Silicotic miners.
[†]Estimate reported in Rice and Stayner [1995].
[‡]Approximate.
[§]Primarily cristobalite dust. Cumulative risk of small opacities ≥ ILO category 1/0 and/or large opacities. For 1,452 workers with an average crystalline silica exposure ≤ 0.50 mg/m^3; 1,138 (78%) of these workers were hired in 1950 or later.
[**]Primarily cristobalite dust. Cumulative risk of small opacities ≥ ILO category 1/0 and/or large opacities. For 357 workers with an average crystalline silica exposure > 0.50 mg/m^3; 319 (89%) of these workers were hired before 1950.
[††]Based on cumulative silica exposure model with 10 yr of post-employment followup.
[‡‡]Nonsilicotic miners.
[§§]No post-employment followup and no retired miners included. The range includes five estimates (one for each reader). Estimate reported in Rice and Stayner [1995].
[***]Based on a 50-year-old worker with cumulative silica exposure of 2 $mg/m^3 \cdot yr$.
[†††]Not reported. Mean duration of employment was 17 yr for all workers and 27.5 yr for workers in the highest category of cumulative silica exposure.
[‡‡‡]ILO category ≥ 1/0. Based on a 40-yr working lifetime and controlling for pack-years of cigarette smoking, race, and silica exposure other than in the foundry under study.
[§§§]Steenland [1998].
[****]Includes 141 cases documented on death certificate only. Estimated risk not adjusted for age or calendar time [Steenland 1997].

Table 13. Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Hnizdo and Sluis-Cremer [1993], South Africa, cohort study	2,235 white underground gold miners who were aged 45 to 54 at time of medical examination in 1968–1971, started working after 1938, worked ≥10 yr, and were followed until 1991.	ILO* category ≥1/1and rounded opacities (313 cases); 23.5 yr for total cohort and 26.9 yr for cases; 36 yr for cases.	30% after heat and acid treatment [Beadle and Bradley 1970].	Cumulative risk	Authors speculated that these silicosis risk estimates were higher than estimates for Canadian miners reported by Muir et al. [1989a,b] and Muir [1991] because (1) dust exposure may have been under-estimated, (2) South African gold mine dust may be more fibrogenic than Canadian mine dust, (3) average proportion of quartz may be >30%, (4) there may have been differences in age at end of radiological follow-up, and (5) exposures for Canadian miners (Hnizdo's [1995] response to Hughes and Weill [1995]) may have been overestimated.

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Hughes et al. [1998], United States, retrospective cohort study	2,342 white male workers employed at least 1 yr between 1942 and 1987 in one diatomaceous mining and processing facility. Exposure-response analyses included the 1,809 men with a radiograph taken more than 1 month after hire.	Small opacities ≥ILO profusion category 1/0 and/or large opacities (81 cases); 5.54 yr[†]; 11.5 yr.	Natural diatomite, 3%; calcined diatomite, 20%; flux-calcined diatomite, 60% (see comments).	Cumulative risk	82 workers had radiographs taken after retirement—development of opacities was not recorded for other workers after they left employment. Quantitative air-monitoring data were available after 1948; respirable dust concentrations before 1948 were estimated [Seixas et al. 1997]. Cumulative risk estimates for radiographic opacities were lower for workers who were hired after 1950 and who had lower average exposures to crystalline silica dust (mainly cristobalite). Estimated percentages of respirable crystalline silica reported by Checkoway et al. [1997] in mortality study of same cohort: 10% for calcined diatomaceous earth, and 20% for flux-calcined diatomaceous earth.

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Kreiss and Zhen [1996], United States, community-based random sample survey	134 male residents of a hardrock[‡] mining town who were aged ≥40: 100 silica-exposed hardrock miners (included 32 silicosis cases) and 34 community controls without occupational dust exposure.	ILO category ≥1/0; 27.6 yr for silicotics and 22.9 yr for nonsilicotic miners; 41.6 yr for silicotics and 33.5 yr for nonsilicotics.	12.3%	Prevalence	Possible overestimation of silicosis risk because of underestimation of pre-1974 dust and silica exposures. Exposures were also estimated for mines where there were no exposure data (17.1% of the person-yr of followup). Risk estimates were presented for models of cumulative silica dust exposure or cumulative dust exposure—the models of cumulative silica dust exposure gave higher estimates. Silicosis (i.e., ≥ category 1/1) risk estimates from models of cumulative dust exposure were similar to estimates for South African gold miners [Hnizdo and Sluis-Cremer 1993] and U.S. gold miners [Steenland and Brown 1995a].

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Muir et al. [1989a,b], Verma et al. [1989], Muir [1991]; Canada; retrospective cohort study	2,109 current Ontario gold and uranium miners who started and worked ≥5 yr between 1940 and 1959 and were followed to 1982 or to the end of their dust exposure, whichever came first.	ILO category ≥1/1 and small, rounded opacities (32 cases); approximately 20 yr; approximately 25 yr (based on interpretation of data in table and graph of Muir et al. [1989b]).	6.0% for gold mine dust; 8.4% for uranium mine dust.	Cumulative risk	Retired and former workers not included, which may have underestimated silicosis risk. Disagreement about silicosis classification among the five readers of the chest X-rays may have "complicated the analysis" [Muir et al. 1989b].

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Ng and Chan [1994], Hong Kong, cross-sectional study	338 current and previous granite workers employed ≥1 yr between 1967 and 1985.	ILO category ≥1/1 (rounded or irregular opacities); 17.4 yr; not reported.	27%	Prevalence	Cumulative risks not calculated. Exposure data for 1976–1981 in one quarry and for 1971–1975 and 1976–1981 in another quarry were not available and were assumed to be the same concentrations measured in 1982 for the period 1976–1981 and in 1971 for the period 1971–1985 [Ng et al. 1987]. Possible underestimate of silicosis risk because decedents were not included.

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Rosenman et al. [1996], United States, cross-sectional study	549 current, 497 retired, and 26 current salaried workers that were former production workers in a gray iron foundry that produced automotive engine blocks (total workers=1,072).	ILO category ≥ 1/0 and rounded opacities (28 cases); 19.2 yr; 28.3 yr.	Not reported.	Prevalence	Prevalence of silicosis cases increased with (1) years of employment, (2) cigarette smoking, (3) mean silica exposure, and (4) cumulative silica exposure. Exposure estimates were derived from conversions of "early silica exposure data" collected by impingers. Underascertainment of silicosis cases is likely because there was no systematic radiologic followup of retired workers. Results showed that African-American workers had two times the risk of radiographic silicosis compared with white workers but a similar duration of employment; however, African-American workers had greater mean exposure to silica dust. When exposure to silica was controlled for in the analysis, the prevalence of radiographic silicosis was similar for African-American workers and white workers.

See footnotes at end of table.

(Continued)

Table 13 (Continued). Summary of epidemiologic studies of silicosis with cumulative dust exposure data and silicosis risk estimates

Reference, country, and study design	Cohort	Definition of silicosis, mean duration of employment, and mean yr since first quartz exposure	Silica (quartz) content of respirable dust	Measure of association	Comments
Steenland and Brown [1995a], United States, cohort study	3,330 white male underground gold miners employed ≥1 yr between 1940 and 1965 and followed through 1990.	Mortality[§] and ILO category ≥1/1 (1976 radiographic survey) or "small opacities" or "large opacities" (1960 radiographic survey) (170 cases); 9 yr; 37 yr.	13% [Zumwalde et al. 1981]	Cumulative risk	Silicosis risk estimates could have been affected by (1) combining silicosis deaths with silicosis cases detected by cross-sectional radiographic surveys, (2) difference in quartz content of dust in early years, (3) lack of dust measurements before 1937.

[*]International Labour Organization.
[†]Median [Checkoway et al. 1997].
[‡]Molybdenum, lead, zinc, and gold mining.
[§]Underlying or contributing cause of death was silicosis, silico-tuberculosis, respiratory tuberculosis, or pneumoconiosis.

A currently unpublished study of 600 retired Vermont granite workers found nodular opacities consistent with silicosis (degrees of profusion not reported in abstract) in 4.7% of 360 radiographs read by three readers [Graham et al. 1998]. The average duration of employment for these workers was 31 years, and the average time from first exposure to radiographic examination was 39 years. Most workers in the cohort were first employed after 1940, when average quartz dust concentrations were below the current OSHA PEL [Graham et al. 1991; Ashe and Bergstrom 1964].

Although the variability in prevalence estimates (i.e., 1% to 90%) cannot be solely attributed to differences in followup periods, chronic silicosis is a progressive disease, and its development after a long latency period and after workers leave employment must be accounted for in epidemiologic studies. A study of autopsied gold miners in South Africa also supports the need for examining workers after a long latency period and after they leave employment [Hnizdo et al. 1993]. Radiologic findings for profusion of rounded opacities (ILO category $\geq$1/1) were compared with pathological findings for silicosis in 326 miners with an average of 2.7 years between the radiologic and pathologic examinations. Silicosis was not diagnosed radiographically for at least 61% of the miners with slight to marked silicosis at autopsy. The probability of a false negative reading increased with years of mining and average concentration of respirable dust [Hnizdo et al. 1993]. Experimental studies of rats also reported a lack of complete agreement between histopathologic indicators of silica dust exposure and radiographic readings [Drew and Kutzman 1984a,b].

In addition, improved exposure assessment methods and data analyses that account for variations and deficiencies in exposure data would improve the risk estimates for silica-exposed workers [Agius et al. 1992; Checkoway 1995]. Although epidemiologic studies that used cumulative exposure estimates represent the best available source of information for characterizing the dose-response relationship in occupational cohorts, peak exposures may predict silicosis risk better than cumulative exposures [Checkoway and Rice 1992]. However, data on peak exposures are rarely available, and data supporting this hypothesis are limited.

3.3 TB and Other Infections

3.3.1 Definition

As silicosis progresses, it may be complicated by severe mycobacterial or fungal infections [NIOSH 1996b; Ziskind et al. 1976; Parkes 1982; Parker 1994]. The most common of these infections, TB, occurs when the macrophages are overwhelmed by silica dust and are unable to kill the infectious organism *Mycobacterium tuberculosis* [Parker 1994; Ng and Chan 1991; NIOSH 1992a,b; Allison and Hart 1968]. About half of the mycobacterial infections that occur in workers with exposure to silica are caused by *M. tuberculosis*, and the other half are caused by the nontuberculous mycobacteria (NTM) *Mycobacterium kansasii* and *Mycobacterium avium-intracellulare* [Owens et al. 1988; NIOSH 1996b]. Infections in workers with silicosis may also be caused by *Nocardia asteroides* and *Cryptococcus* [Ziskind et al. 1976; NIOSH 1996b; Parker 1994; Parker and Wagner 1998]. ATS [1997] recommends that the diagnostic investigation of a patient with silicosis and possible TB include consideration of NTM disease. The ATS also recommends that tuberculin tests be administered to persons with silicosis and to those without silicosis who have at least 25 years of occupational exposure to crystalline silica [ATS 1997].

3.3.2 Epidemiologic Studies

Recent surveillance data indicate that TB rates in the United States are 5 to 10 times higher

among racial and ethnic minorities (after adjustment for the effects of age, sex, and country of birth) [Cantwell et al. 1998]. Cantwell et al. [1998] reported that the relative risk of TB increased as socioeconomic status (measured by six indicators) decreased, after adjustment for the effects of age (relative risks ranged from 2.6 to 5.6 in the lowest versus highest quartiles). The number of TB cases among foreign-born persons in the United States increased by 56% during the period 1986 to 1997 [CDC 1998c].

The association between TB and silicosis has been firmly established by the results of epidemiologic studies conducted during this century [Balmes 1990]. This association was supported by a survey of TB deaths among silicotics in the United States for the period 1979 to 1991 [Althouse et al. 1995] and by the results of four recent epidemiologic studies [Goldsmith et al. 1995; Cowie 1994; Sherson and Lander 1990; Kleinschmidt and Churchyard 1997]. Black South African gold miners [Cowie 1994] and Danish foundry workers [Sherson and Lander 1990] with chronic silicosis had threefold and tenfold incidences of TB, respectively, compared with nonsilicotic, non-silica-exposed workers of similar age and race. Goldsmith et al. [1995] compared the mortality of 590 California silicosis claimants with that of U.S. males and found that the TB mortality of the claimants was 50 times that of all U.S. males (standardized mortality ratio [SMR]=56.35; 45 deaths observed, 0.8 expected; 95% confidence interval [CI]=41.10–75.40). A retrospective study of TB among 4,976 miners from the Freegold mines in South Africa reported that the incidence rate ratio for miners with silicosis (ILO category $\geq$1/1) was 1.54 (95% CI=1.00–2.37) compared with miners without silicosis (after adjusting for the effects of age, followup period, cumulative service, and occupation) [Kleinschmidt and Churchyard 1997]. The incidence of TB for the oldest age group was 21 times that of the youngest group (incidence rate ratio=21.17; 95% CI=8.60–52.11); and for workers in occupations with high dust exposure (such as drilling), the incidence was twice that of surface and maintenance workers (adjusted incidence rate ratio=2.25; 95% CI=1.49–3.38) [Kleinschmidt and Churchyard 1997].

Some evidence indicates that workers who do not have silicosis but who have had long exposures to silica dust may be at increased risk of developing TB. Two epidemiologic studies reported that, compared with the general population, a threefold incidence of TB cases occurred among 5,424 nonsilicotic, silica-exposed Danish foundry workers employed 25 or more years [Sherson and Lander 1990], and nearly a tenfold incidence occurred among 335 nonsilicotic, black South African gold miners with a median underground employment of 26 years [Cowie 1994].

Westerholm et al. [1986] found 13 cases among 428 silicotic Swedish iron and steel workers and 1 case in a comparison group of 476 Swedish iron and steel workers with normal chest radiographs (level of statistical significance not reported). Both groups had been exposed to silica for at least 5 years.

A study of TB incidence in 2,255 white South African gold miners included 1,296 miners who had an autopsy [Hnizdo and Murray 1998, 1999]. The smoking-adjusted relative risk for TB in miners without silicotic nodules on autopsy examination (n=577) increased slightly with quartiles of cumulative dust exposure (relative risk=1.38 [95% CI=0.33–5.62] for the highest quartile of cumulative exposure). For miners without radiologically diagnosed silicosis (n=1,934), the smoking-adjusted relative risk increased to 4.01 (95% CI=2.04–7.88) in the highest quartile of cumulative dust exposure [Hnizdo and Murray 1998, 1999]. The authors defined radiologic silicosis as ILO category $\geq$1/1. TB was diagnosed, on the average, 7.6 years after the end of dust exposure and

6.8 years after the onset of radiological silicosis—a result that supports the need for medical surveillance of workers after the end of exposure to silica dust [Hnizdo and Murray 1998]. Miners who developed TB before completing 10 years of underground employment were excluded because they were not allowed to continue working underground after diagnosis.

Corbett et al. [1999] conducted a recent case-control study of TB and pulmonary disease caused by NTM in South African gold miners. These researchers found that radiographic silicosis, focal radiological scarring, and human immunodeficiency virus (HIV) infection were significant risk factors for NTM disease and for TB. Past medical history of TB treatment (odds ratio [OR]=15.1; 95% CI=7.64–29.93) and current employment in a "dusty job" at the mines (OR=2.5; 95% CI=1.46–4.44) were significant risk factors for NTM. ORs for NTM and TB increased with years of employment (range of ORs was 1.0 to 9.4 for NTM and 1.0 to 4.1 for TB). The study included 206 NTM patients and 381 TB patients of known HIV status admitted to a South African hospital. Also included were 180 controls who were HIV-tested surgical or trauma patients admitted to the same hospital during the same period.

Two recent studies about silica exposure and TB used U.S. occupational mortality data to conduct a proportionate mortality study of persons with TB by occupation for 1979 through 1990 [CDC 1995; Chen et al. 1997]. Although the study design did not control for confounding, it identified six occupational groups with potential exposure to silica dust that had age-adjusted proportionate mortality ratios (PMRs) for TB that were statistically significant (lower bound of the 95% CI>100) or greater than 200. Table 14 shows significant PMRs by race for construction occupations, mining machine operators, grinding and polishing machine operators, furnace and kiln operators, laborers, and mixing and blending machine operators [CDC 1995].

Chen et al. [1997] conducted a case-control study (8,740 cases; 83,338 controls) with U.S. National Occupational Mortality Surveillance (NOMS) data for 1983–1992. The study controlled for confounding from age, sex, race, socioeconomic status, potential exposure to active TB, and the presence of silicosis and other pneumoconioses. The potential for silica exposure was based on data from NOES [NIOSH 1988] and the National Occupational Health Survey of Mining (NOHSM) [NIOSH 1996c]. This potential was categorized as "high," "intermediate," or "low or no." The study found that decedents with high potential for exposure to silica and no documentation of silicosis on the death certificate had a 30% greater odds of mortality from respiratory TB than decedents with no potential exposure to silica after adjustment by logistic regression for the possible confounders mentioned earlier (OR=1.3; 95% CI=1.14–1.48). The results also suggest an exposure-response relationship between silica exposure (in the absence of silicosis) and death from respiratory tuberculosis [Chen et al. 1997].

3.4 Cancer

3.4.1 Background

The possible carcinogenicity of crystalline silica dust became a subject of considerable and intense debate in the scientific community in the 1980s, especially after (1) publication of new information presented at a 1984 symposium in North Carolina [Goldsmith et al. 1986], (2) epidemiologic studies by Westerholm [1980] and Finkelstein et al. [1982], and (3) a literature review by Goldsmith et al. [1982] (see McDonald [1989, 1995] and Graham [1998]). Many epidemiologic studies of cancer mortality and morbidity in silica-exposed occupational groups were published

Table 14. Selected age-adjusted PMRs[*,†] for pulmonary TB by usual occupation, sex, and race in 28 States, 1979–1990

Occupation of decedent and 1980 census code	Male decedents						Female decedents					
	White			Black			White			Black		
	Number	PMR	95% CI	Number	PMR	95% CI	Number	PMR	95% CI	Number	PMR	95% CI
Construction occupations (553–599, 865, and 869)	169	134[†]	114–156	105	128[†]	104–155	0	—	—	0	—	—
Brick and stone mason (553 and 563–564)	12	213[†]	110–371	11	159	80–285	0	—	—	0	—	—
Carpenter (554, 567, and 569)	50	147[†]	109–194	9	97	44–184	0	—	—	0	—	—
Roofer (595)	6	290[†]	106–630	1	53	1–293	0	—	—	0	—	—
Construction laborer (869)	34	175[†]	121–244	61	156[†]	120–201	0	—	—	0	—	—
Mining machine operator (616)	54	276[†]	207–360	4	128	35–328	0	—	—	0	—	—
Grinding, abrading, buffing, or polishing machine operator (709)	7	265[†]	107–547	1	94	2–523	0	—	—	0	—	—
Mixing or blending machine operator (756)	1	58	2–326	5	376[†]	122–878	0	—	—	0	—	—
Furnace, kiln, or oven operator, except food (766)	1	27	1–153	5	206[†]	67–481	0	—	—	1	15,000	372–82,842
Laborer, except construction (889)	85	159[†]	127–196	92	111	89–136	12	162	84–283	8	147	64–291

Source: Adapted from CDC [1995]. This data file includes death records from 28 States (Alaska, California, Colorado, Georgia, Idaho, Indiana, Kansas, Kentucky, Maine, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Utah, Vermont, Washington, West Virginia, and Wisconsin).

[*]Abbreviations: PMRs = proportionate mortality ratios; TB = tuberculosis; CI = confidence interval.

[†]Selection criteria: (1) at least four TB deaths in race- and sex-specific group and (2) either a PMR >200 or a PMR with a 95% CI excluding 100.

later, but the issue remained unresolved. In October 1996, an IARC expert working group reviewed the published experimental and epidemiologic studies of cancer in animals and workers exposed to respirable crystalline silica. The working group concluded that there is "sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources" [IARC 1997]. In June 1996, the directors of the ATS adopted an official statement of their Committee of the Scientific Assembly on Environmental and Occupational Health. This statement, prepared at the request of the American Lung Association Occupational Health Expert Advisory Group [ATS 1997], described the adverse health effects of exposure to crystalline silica, including lung cancer. The ATS found the following:

- The available data support the conclusion that silicosis produces increased risk for bronchogenic carcinoma.
- However, less information is available for lung cancer risk among silicotics who never smoked and workers who were exposed to silica but did not have silicosis.
- Whether silica exposure is associated with lung cancer in the absence of silicosis is less clear.

NIOSH concurs with the conclusions of the IARC working group and the ATS. These conclusions agree with NIOSH testimony to OSHA, in which NIOSH recommended that crystalline silica be considered a potentional occupational carcinogen [54 Fed. Reg. 2521 (1989)].

This section, like the IARC review, focuses on lung cancer and discusses the epidemiologic studies that were the least likely to have results affected by confounding and selection biases. In "mixed" environments such as ceramics, pottery, or brick manufacturing, where exposure may be to two or more polymorphs of crystalline silica, epidemiologic studies have usually not identified specific exposures to quartz or cristobalite. Therefore, excess lung cancers that occurred in these environments cannot be associated with exposure to a given polymorph but only with exposure to respirable crystalline silica. The epidemiologic studies of cancer have mainly investigated workers exposed to respirable crystalline silica in (1) ore mining, (2) quarrying and granite works, (3) ceramics, pottery, glass, refractory brick, and diatomaceous earth industries, or (4) foundries. The other major study group was workers with silicosis, usually identified from national or local registries. Studies of workers and silicotics that were not discussed in this document because they failed to meet the "least confounded" criterion have been criticized for the following reasons [Checkoway 1995; McDonald 1995, 1996; Morgan and Reger 1995; Weill and McDonald 1996; Seaton 1995; Weill et al. 1994; Agius et al. 1992]:

- Inadequate, incomplete, or invalid exposure assessment
- Potential selection and confounding biases in the cohort studies of compensated silicotics
- Inadequate control of confounding from cigarette smoking and from concurrent workplace exposures (e.g., potential exposure to radon progeny, arsenic, or diesel exhaust in ore mines and potential exposure to polycyclic aromatic hydrocarbons in foundries)
- Inability to distinguish differences in fibrogenic and carcinogenic potencies of the various silica polymorphs
- Lack of evidence of an exposure-response relationship

3.4.2 Epidemiologic Studies of Lung Cancer

Following a comprehensive review of the large body of published epidemiologic studies, IARC [1997] found that the following studies provide the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer:

1. U.S. gold miners [Steenland and Brown 1995b]
2. Danish stone industry workers [Guénel et al. 1989]
3. U.S. granite shed and quarry workers [Costello and Graham 1988]
4. U.S. crushed stone industry workers [Costello et al. 1995]
5. U.S. diatomaceous earth industry workers [Checkoway et al. 1993, 1996]
6. Chinese refractory brick workers [Dong et al. 1995]
7. Italian refractory brick workers [Merlo et al. 1991; Puntoni et al. 1988]
8. U.K. pottery workers [McDonald et al. 1995,1997; Cherry et al. 1995,1997; Burgess et al. 1997]
9. Chinese pottery workers [McLaughlin et al. 1992]
10. Cohorts of registered silicotics from North Carolina [Amandus et al. 1991,1992] and Finland [Kurppa et al. 1986; Partanen et al. 1994]

Although a few of these studies did not find a statistically significant association between occupational exposure to crystalline silica and lung cancer (Table 15), most of the studies did. Study results are often not uniform when a large number of epidemiologic studies are reviewed and a variety of populations and work environments are studied [IARC 1997]. In addition, IARC noted that the carcinogenicity of quartz or cristobalite "may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs" [IARC 1997].

Some of the least confounded studies reported that lung cancer risk tended to increase with

- cumulative exposure to respirable silica [i.e., Checkoway et al. 1993, 1996],
- duration of exposure [i.e., Merlo et al. 1991; Partanen et al. 1994; Costello and Graham 1988; Costello et al. 1995; Dong et al. 1995],
- peak intensity of exposure [Burgess et al. 1997; Cherry et al. 1997; McDonald et al. 1997],
- the presence of radiographically defined silicosis [Amandus et al. 1992; Dong et al.1995], and
- length of followup time from date of silicosis diagnosis [Partanen et al. 1994] (see Table 15).

These observed associations, including the exposure-response associations, are unlikely to be explained by confounding or other biases. Thus overall, the epidemiologic studies support increased lung cancer risks from occupational exposure to inhaled crystalline silica (i.e., quartz and cristobalite) [IARC 1997].

3.4.2.1 Updated or New Studies Since the IARC Review

Two studies discussed in this section have recently been updated: Checkoway et al. [1997, 1999] updated their previous mortality studies

Table 15. IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Amandus et al. [1991], United States	Mortality study of 714 male, North Carolina dusty trades workers diagnosed with silicosis between 1940 and 1983 and compared with the 1940–1983 lung cancer mortality rates for U.S. males.	Whites	33	2.6	1.8–3.6	Yes	The age- and smoking-adjusted rate ratio for white silicotics with lung cancer was 3.9 (95% CI= 2.4–6.4) compared with a referent group of metal miners.
		Nonwhites	1	0.7	Not reported		
		White silicotics:					
		Diagnosed while employed	28	2.5	1.7–3.7		
		Employed in jobs with silica exposure only§	26	2.3	1.5–3.4		"Exposure to respirable silica dust" was defined as working in a dusty trade and having radiographic silicosis.
		Past or current smokers	18	3.4	2.0–5.3		
		Silicotics, never smoked	5	1.7	0.5–3.9		No quantitative exposure data were available.
Amandus et al. [1992], United States	Mortality study of subgroup of 306 white males from Amandus et al. [1991] cohort of silicotics diagnosed and traced from 1940 through 1983. 143 of the subgroup were reclassified as silicotics, and 96 were reclassified as having a normal radiograph. 10 deaths from lung cancer occurred in the reclassified group.	Silicotics	8	2.5	1.1–4.9	Yes	"Exposure to respirable silica dust" was defined as working in a dusty trade and having radiographic silicosis.
		Nonsilicotics**	2	1.0	0.1–3.5		
		Smokers:					
		Silicotics	5	3.4	1.1–7.9		
		Nonsilicotics**	1	1.3	0.03–7.1		No quantitative exposure data were available.

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Burgess et al. [1997], Cherry et al. [1997], McDonald et al. [1997], United Kingdom	Nested case-control study of lung cancer deaths within Cherry et al. [1995], including duration and intensity of exposure, smoking, and radiological changes. Cases were employed as pottery workers for ≥10 yr. Each death was matched with 3 or 4 controls on date of birth and date of first exposure.	Cumulative exposure to respirable crystalline silica dust ≥4,000 μg/m³·yr	52	0.60††	0.26–1.41‡‡	Yes	ORs were adjusted for smoking and radiographic changes.
		Duration of employment ≥20 yr	—	0.48††	0.21–1.09‡‡		This was the only epidemiologic study of peak exposure effects and lung cancer. Results support significant lung cancer risk for high-intensity silica exposures.
		Mean intensity of silica dust exposure ≥200 μg/m³	—	1.68††	0.93–3.03‡‡		
		Maximum silica dust exposure ≥400 μg/m³	—	2.07††	1.04–4.14‡‡		Silica dust exposures ≥400 μg/m³ occurred in firing and post-firing operations. Exposures to cristobalite were possible.

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Checkoway et al. [1993; 1996], United States	Mortality study of 2,570 male workers at diatomaceous earth plants employed ≥ 1 yr and worked ≥ 1 day between 1942 and 1987. Cohort mortality traced for that period.	—	59	1.43	1.09–1.84	Limited to comparisons of smoking prevalence.	Estimated relative risks for lung cancer (not shown) were adjusted for age, calendar year, duration of followup, and ethnicity. The risks increased significantly ($P \leq 0.05$ for trend) with duration of employment and cumulative exposure to crystalline silica [Checkoway et al. 1993]. Checkoway et al. [1996] also adjusted for asbestos exposure.
	Checkoway et al. [1996] reanalyzed 2,266 workers (a subset of the original cohort). Mortality traced from 1942 through 1987.	—	52	1.41	1.05–1.85		
Cherry et al. [1995], United Kingdom	Mortality study of 5,115 pottery workers, excluding exposure to asbestos, foundry, and other dusts; with mortality followup to June 30, 1992.	—	68	1.28	1.04–1.57‡‡	No	Lung cancer rates in pottery workers were compared with local mortality rates.

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Costello and Graham [1988], United States	Mortality study of 5,414 white male workers in Vermont granite sheds and quarries employed between 1950 and 1982 with at least one radiologic examination in the worker surveillance program.	Quarry workers	20	0.82	Not reported	No	Dust exposure data were not included, limiting conclusions about exposure-response. Cohort overlaps with cohort of Davis et al. [1983]. CIs reported by IARC [1997].
		Shed workers:	98	1.27	Not reported§§		
		Started before 1940, latency period ≥40 yr, tenure ≥30 yr	47	1.81	1.33–2.41***		
		Started after 1940, latency period ≥25 yr, tenure ≥10 yr	17	1.73	1.01–2.77		
Costello et al. [1995], United States	Mortality study of 3,246 male workers employed ≥1 yr between 1940 and 1980 at 20 U.S. crushed stone (i.e., granite, limestone, traprock, or sandstone) operations.	Whites	40	1.2	0.9–1.6	No	—
		Nonwhites	11	1.9	0.9–3.3		
		Workers in granite facilities with ≥20-yr latency period and ≥10-yr tenure	7	3.5	1.4–7.3		
		Workers in limestone facilities	23	1.5	1.0–2.3		
		Workers in traprock facilities	3	0.6	0.1–1.8		

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Dong et al. [1995], China	Mortality study of lung cancer in 6,266 male silicotic and nonsilicotic refractory brick workers employed before 1962 and followed for mortality from 1963 to 1985. 11,470 nonsilicotic male steel workers used as controls.	Silicotics	35	2.1†††	Not reported***	Yes	Twofold excess lung cancer mortality occurred in both smokers and nonsmokers. Exposure-response trends were found for years since first employment and lung cancer mortality, and for severity of silicosis and lung cancer mortality.
		Silicotics in Chinese radiological category:					
		I	21	2.0	Not reported***		
		II	10	2.3	Not reported§§		
		III	4	2.6	Not reported§§		
		Nonsilicotics	30	1.1	Not reported***		
Guénel et al. [1989], Denmark	Cohort study of 2,175 Danish stone workers who met the following criteria: • were alive on Jan. 1, 1943, or were born later, and • were aged <65 when first identified in one of 6 data sources. The cohort included 2,071 cancer cases identified in the Danish cancer registry between 1943 and 1984.	Lung cancer cases	44	2.00‡‡‡	1.49–2.69	Yes	Adjusted for regional differences in smoking. Lung cancer mortality highest among Copenhagen sandstone cutters hired before 1940 prior to ventilation improvements.

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure*	CI†	Smoking information available and analyzed	Comments
McDonald et al. [1995], United Kingdom	Preliminary report of proportionate mortality study of 7,020 pottery workers born between 1916 and 1945 with mortality followup to June 30, 1992. Preliminary nested case-control study of 75 lung cancer cases and 75 controls.	Lung cancer deaths in pottery workers not exposed to asbestos	112	1.22§§§	1.04–1.43‡‡	No	Preliminary results (final results in Cherry et al. [1995]).
		Smokers and nonsmokers with ≥10 yr of silica exposure	75	1.4††	0.7–2.7‡‡		Lung cancer rates in pottery workers were compared with local mortality rates.
		Smokers with ≥10 yr of silica exposure	47	2.8††	1.1–7.5‡‡		
McLaughlin et al. [1992], China	Nested case-control study of 62 pottery factory workers employed between 1972 and 1974 who died from lung cancer before 1990; 238 controls matched by decade of birth and factory.	Cumulative respirable silica dust exposure (μg/m3·yr):				Yes	ORs were adjusted for age and smoking. Test for exposure-response trend was not statistically significant (P>0.05) for cumulative exposure to dust or respirable silica. High OR (7.4; CI and number of deaths not reported) for lung cancer in workers who smoked >20 cigarettes per day. CIs reported in IARC monograph [1997].
		None	11	1.0	—		
		Low (0.1–8.69)	17	1.8	1.04–2.87		
		Medium (8.70–26.2)	27	1.5	0.99–2.18		
		High (≥26.3)	7	2.1	0.80–4.12		

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Merlo et al. [1991], Italy	1,022 male refractory brick workers employed at least 6 months between 1954 and 1977. Retrospective cohort study of mortality through 1986.	All brick workers	28	1.51	1.00–2.18	Yes	Smoking habits of cohort comparable with the national population (includes the men in Puntoni et al. [1988]).
		Brick workers:					
		≤19 yr since 1st exposure and employed ≤19 yr	7	1.05	0.42–2.16		
		>19 yr since 1st exposure and employed ≤19 yr	8	1.75	0.75–3.46		
		>19 yr since 1st exposure and employed >19 yr	13	2.01	1.07–3.44		

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Partanen et al. [1994], Finland	Cohort study of 811 male silicotics, compensated and not compensated, who were diagnosed between 1936 and 1977 in Finland. Cancer incidence for 1953–1991 was obtained from the Finnish Cancer Registry.	Length of followup from date of silicosis diagnosis:				Yes	Update of Kurppa et al. [1986].
		<2 yr	1	0.4§§§	0.01–2.3		
		2–9 yr	32	2.7	1.9–3.9		No evidence of confounding by tobacco smoking.
		≥ 10 yr	168	3.3	2.5–4.1		
		Histology of lung cancers:					
		Adenocarcinoma	5	2.0	0.6–4.6		
		Squamous-cell	34	3.2	2.3–4.5		
		Small-cell	9	2.1	0.9–3.9		
		Other/unknown	53	3.0	2.2–3.9		
		Industry:					
		Mining/quarrying (excluding granite)	38	3.7	2.6–5.0		
		Granite	13	2.9	1.6–5.0		
		Glass/ceramic	10	3.3	1.6–6.1		
		Grinding/sharpening	3	3.0	.6–8.7		
		Casting/founding	22	1.8	1.1–2.6		
		Construction	2	10	1.3–37		
		Excavation/foundation	9	5.8	2.7–11.1		

See footnotes at end of table.

(Continued)

Table 15 (Continued). IARC*-reviewed epidemiologic studies having the least confounded investigations of an association between occupational exposure to crystalline silica and lung cancer

Reference and country	Study design, cohort, and followup	Subgroup	Number of lung cancer deaths or cases	Risk measure†	CI‡	Smoking information available and analyzed	Comments
Steenland and Brown [1995b], United States	Cohort study of 3,328 white male gold miners employed underground ≥ 1 yr between 1940 and 1965 and followed for mortality from 1977 to 1990. Mortality rates of U.S. males used for comparison.	—	115	1.13	0.94–1.36	Yes	High historical exposures. No exposure-response trend by cumulative dust exposure. Low radon and arsenic exposures.

Source: IARC [1997].

*Abbreviations: CI=confidence interval; IARC=International Agency for Research on Cancer; PMR=proportional mortality ratio; OR=odds ratio; SIR=standardized incidence ratio; SMR=standardized mortality ratio; SRR=standardized rate ratio

†SMR unless otherwise noted.

‡95% CI unless otherwise noted.

§Workers who had no known exposure to other occupational carcinogens such as asbestos manufacturing, insulation work, olivine mining, talc, and foundry work.

**Nonsilicotics are subjects with normal radiographs.

††OR.

‡‡90% CI.

§§$P < 0.05$.

***$P < 0.01$.

†††Values in this study are SRRs.

‡‡‡Values in this study are SIRs.

§§§PMR.

of diatomaceous earth workers [Checkoway et al. 1993, 1996] by including deaths after 1987 and through 1994, and by analyzing lung cancer risk among workers with radiographic silicosis. Lung cancer mortality risk was highest in the highest category of cumulative exposure to respirable crystalline silica (rate ratio with no exposure lag period=2.11; 95% CI=1.07–4.1; rate ratio for 15-year exposure lag period=1.05; 95% CI=0.99–1.11). The rate ratios were adjusted for the effects of age, calendar year, duration of followup, and ethnicity. Among workers with radiological silicosis (ILO category ≥1/0 or large opacity; n=81), the lung cancer SMR was 1.57 (95% CI= 0.43–4.03) [Checkoway et al. 1999]. For workers without silicosis (ILO category <1/0), the SMR was 1.19 (95% CI=0.87–1.57). The SMRs were adjusted for age and calendar year and were based on the expected number of deaths for white U.S. males. For the nonsilicotic workers, a statistically significant, positive dose-response relationship (P=0.02) was observed between SMRs for lung cancer and category of cumulative respirable silica exposure. The SMRs ranged from 1.05 in the lowest exposure category (<0.5 mg/m^3· year, 13 deaths, 95% CI=0.56–1.79) to 2.40 in the highest exposure category (≥5.0 mg/m^3 · year; 12 deaths, 95% CI=1.24–4.20). For the 81 workers with radiographic silicosis, an SMR >1.0 was observed only in the highest exposure category (i.e., ≥5.0 mg/m^3 · year) (4 deaths observed; SMR=2.94; 95% CI=0.80–7.53). These results suggest that silicosis may not be a necessary condition for silica-related lung cancer. However, radiographic surveillance of this cohort did not extend beyond the dates of employment termination, and autopsies were not routinely conducted [Checkoway et al. 1999].

Cherry et al. [1998] finalized the preliminary results of a nested case-control study of 52 lung cancer deaths in 5,115 pottery workers (see Burgess et al. [1997], Cherry et al. [1997], and McDonald et al. [1997] in Table 15). After adjustment for smoking and inclusion of a 20-, 10-, or 0-year lag period, mean respirable silica concentration (i.e., estimated daily 8-hr TWA airborne concentrations in µg/m^3) was associated with lung cancer (P<0.008 for each lag period):

Lag	*OR*	*95% CI*
20 yr	1.60	1.11–2.31
10 yr	1.66	1.14–2.41
0 yr	1.67	1.13–2.47

However, exposure duration and cumulative silica dust exposure were not significantly associated with lung cancer mortality, regardless of lag time [Cherry et al. 1998]. The presence of small, parenchymal radiographic opacities (ILO category ≥1/0) was not related to lung cancer mortality before adjustment for smoking (P=0.78) or after adjustment for smoking and mean silica concentration (P=0.68). The authors concluded "that crystalline silica may well be a human carcinogen" [Cherry et al. 1998].

Other studies published since the IARC review also investigated exposure-response associations for lung cancer and exposure to crystalline silica. Rafnsson and Gunnarsdóttir [1997] reported that the incidence of lung cancer cases among 1,346 diatomaceous earth workers in Iceland was not statistically significant for workers who had 9 years before start of followup and who were employed ≥5 years (standardized incidence ratio [SIR] based on 3 cases observed=2.70; 95% CI=0.56–7.90) or employed ≤5 years (SIR based on 2 cases observed=1.19; 95% CI=0.14–4.30).

de Klerk and Musk [1998] conducted a cohort study of 2,297 surface and underground gold miners in western Australia who participated in surveys of respiratory symptoms, smoking habits, and lung function in 1961, 1974, and 1975. Eighty-nine percent of the cohort was

traced to the end of 1993 for trachea, bronchus, and lung cancer mortality and incidence of compensated silicosis (i.e., compensation awarded by the Pneumoconiosis Medical Board). A nested case-control analysis of the 138 lung cancer deaths found that lung cancer mortality was related to log total cumulative silica dust exposure after adjustment for smoking (cigarette, pipe, or cigar) and for the presence of bronchitis at survey (relative rate=1.31; 95% CI=1.01–1.70). However, the effect of cumulative silica dust exposure on lung cancer mortality was not significant after adjustment for smoking, bronchitis, and compensation for silicosis (relative rate=1.20; 95% CI=0.92–1.56). Other silica exposure variables (i.e., duration of underground or surface employment and intensity of underground or surface exposure) were not significantly related to lung cancer mortality (P>0.15) after adjustment for smoking and bronchitis. Cigarette smoking (relative rate=32.5; 95% CI=4.4–241.2 for ≥25 cigarettes smoked per day), incidence of a compensation award for silicosis after lung cancer diagnosis (relative rate=1.59; 95% CI=1.10–2.28), and presence of bronchitis at survey (relative rate=1.60; 95% CI=1.09–2.33) were significantly related to lung cancer mortality [de Klerk and Musk 1998]. The results of this study do not support a relationship between lung cancer and silica exposure in the absence of silicosis (i.e., a compensation award for silicosis after lung cancer diagnosis). However, controlling for silicosis compensation and bronchitis may have masked a silica effect because both are markers of silica exposure.

Hnizdo et al. [1997] conducted a nested case-control study of lung cancer deaths in a cohort of 2,260 white South African underground gold miners. (A lung cancer mortality cohort study had been conducted earlier [Hnizdo and Sluis-Cremer 1991]). The mineral content of the rock in the gold mines was mostly quartz (70%–90%), silicates (10%–30%), pyrite (1%–4%), and heavy minerals with grains of gold and uranium-bearing minerals (2%–4%). Seventy-eight miners who died from lung cancer (69 of the 78 had a necropsy) during 1970–1986 were matched by year of birth with 386 control subjects from the same cohort [Hnizdo et al. 1997]. Conditional logistic regression models were used to analyze the relationship of lung cancer mortality with cigarette smoking (pack-years), cumulative "dust" exposure (mg/m^3 · year), years of underground mining, incidence of radiographic silicosis (ILO category ≥1/1 diagnosed up to 3 years before death of a matched case), and uranium production or uranium grade of the ore in the gold mine. Radon progeny measurements in the gold mines were not available.

Lung cancer mortality was associated with cigarette smoking, cumulative dust exposure (lag time was 20 years from death), duration of underground mining (lag time was 20 years from death), and silicosis. The best-fitting model predicted relative risks of 2.45 (95% CI= 1.2–5.2) for silicosis and the following relative risks for various pack-years of smoking:

Pack-years	*95% CI*	*Relative risk*
<6.5	—	1
6.5–20	0.7–16.8	3.5
21–30	1.3–25.8	5.7
>30	3.1–56.2	13 .2

The authors stated that variables representing uranium mining were not significantly related to lung cancer mortality (modeling results for these variables were not presented) [Hnizdo et al. 1997]. The authors proposed three explanations for their results:

- Miners with high dust exposure who develop silicosis have increased lung cancer risk.

- High silica dust exposure concentrations are important in the pathogenesis of lung cancer, and silicosis is coincidental.

- High silica dust exposure concentrations are a surrogate measure of exposure to radon progeny [Hnizdo et al. 1997].

3.4.2.2 Lung Cancer Meta-Analyses

Meta-analysis and other systematic literature review methods are useful tools for summarizing exposure risk estimates from a large amount of information [Mulrow 1994]. Meta-analyses or summary reviews of epidemiologic studies of silicotics with lung cancer have been conducted by investigators in the United States [Steenland and Stayner 1997; Smith et al. 1995] and Japan [Tsuda et al. 1997]. IARC is performing a pooled analysis of epidemiologic data from several cohorts to investigate lung cancer risks in nonsilicotic workers.

Steenland and Stayner [1997] and IARC [1997] found that the majority of studies of silicotics reported statistically significant excess lung cancer risks across different countries, industries, and time periods while controlling for the effects of cigarette smoking [Steenland and Stayner 1997; IARC 1997]. Exposure-response gradients were also observed. The summary relative risk was 2.3 (95% CI=2.2–2.6) for 19 cohort and case-control studies of silicotics—excluding studies of miners and foundry workers because of potential exposure to other carcinogens, and omitting autopsy studies and proportionate mortality studies because of possible selection biases [Steenland and Stayner 1997]. Fifteen of the 19 studies directly or indirectly controlled for the effects of smoking. The summary relative risk of 16 cohort* and case-control studies of silica-exposed workers was 1.3 (95% CI= 1.2–1.4)—a moderate and statistically significant relative risk estimate [Steenland and Stayner 1997]. Eight of the 16 studies controlled for the effects of smoking, either directly or indirectly.

Another meta-analysis of 23 lung cancer studies of silicotics (including 14 of the studies analyzed by Steenland and Stayner [1997]) reported a pooled risk estimate of 2.2 (95% CI= 2.1–2.4) [Smith et al. 1995]. The statistically significant pooled risk estimates from both meta-analyses strongly support an association between silicosis and lung cancer. The increased risk of lung cancer for silicotics is also supported by the following [IARC 1997]:

1. The magnitude of the risk estimates (i.e., most studies reported risks greater than 2.0 for silicotics after adjusting for the effects of cigarette smoking—compared with exposed nonsilicotics or the general population)

2. The observation of exposure-response gradients with various indicators of exposure

3. Consistent findings of excess risk in different countries, industries, and time periods

4. Two studies that provided reasonable evidence for an unconfounded association (i.e., Amandus et al. [1991, 1992, 1995] and Partanen et al. [1994], an update of Kurppa et al. [1986])

Tsuda et al. [1997] conducted a lung cancer meta-analysis of pneumoconiosis or silicosis studies (excluding asbestosis). Lung cancer risk estimates were pooled from 32 mortality studies published from 1980 to 1994. The estimated rate ratios were similar to those reported by Steenland and Stayner [1997] and Smith et al. [1995]:

*Cohort size ranged from 969 to 6,266 workers.

	Rate ratio	*95% CI*
All studies (32[†])	2.74	2.60–2.90
Cohort studies only (25 of 32)	2.77	2.61–2.94
Case-control studies (5 of 32)	2.84	2.25–3.59

3.4.3 Other Cancers

Mortality studies of workers have reported statistically significant excesses of deaths from stomach or gastric cancer in iron ore miners [St. Clair Renard 1984; Lawler et al. 1985; Mur et al. 1987], Canadian gold miners [Muller et al. 1983; Shannon et al. 1987; Miller et al. 1987; Kusiak et al. 1993b], lead and zinc miners [Belli et al. 1989], brick production workers [Katsnelson and Mokronosova 1979], foundry and other metal workers [Neuberger and Kundi 1990], jewelry workers [Hayes et al. 1993; Dubrow and Gute 1987; Sparks and Wegman 1980], farmers (reviewed by Blair and Zahm [1991]), and farm workers [Stubbs et al. 1984] (reviewed by Zahm and Blair [1993]). A recent case-control study of 250 male hospital patients in Canada found a statistically significant excess of pathologically confirmed stomach cancer among the 25 patients who reported a history of "substantial" occupational exposure to crystalline silica compared with 2,822 controls (OR=1.7; 95% CI=1.1–2.7 after adjusting for the effects of age, birthplace, education, and cigarette smoking) [Parent et al. 1998]. However, in a review of epidemiologic studies of gastric cancer and dusty occupations, Cocco et al. [1996] noted that because most studies did not adjust for the effects of confounding factors or assess a dose-response relationship, evidence was insufficient to conclude that silica is a gastric carcinogen.

[†]Two of the studies are proportionate mortality studies for which rate ratios were not reported.

For workers who may have been exposed to crystalline silica, there have been infrequent reports of statistically significant excesses of deaths or cases of other cancers such as nasopharyngeal or pharyngeal cancer [Chen et al. 1992; Carta et al. 1991], salivary gland cancer [Zheng et al. 1996], liver cancer [Chen et al. 1992; Hua et al. 1992], bone cancer [Forastiere et al. 1989; Steenland and Beaumont 1986], pancreatic cancer [Kauppinen et al. 1995], skin cancer [Partanen et al. 1994; Rafnsson and Gunnarsdóttir 1997], esophageal cancer [Pan et al. 1999; Xu et al. 1996; Belli et al. 1989], cancers of the digestive system [Decoufle and Wood 1979], intestinal or peritoneal cancer [Amandus et al. 1991; Goldsmith et al. 1995; Costello et al. 1995], lymphopoietic or hematopoietic cancers [Redmond et al. 1981; Silverstein et al. 1986; Steenland and Brown 1995b], brain cancer [Rafnsson and Gunnarsdóttir 1997], and bladder cancer [Bravo et al. 1987]. Again, an association has not been established between these cancers and exposure to crystalline silica.

3.5 Other Nonmalignant Respiratory Diseases and Related Conditions

3.5.1 COPD

3.5.1.1 Definition

COPD describes chronic airflow limitation that is usually irreversible [ATS 1987; Becklake 1992; Snider 1989]. COPD includes four interrelated disease processes: chronic bronchitis, emphysema, asthma [Barnhart 1994; Snider 1989], and peripheral airways disease [ATS 1987]. Cigarette smoking is a major cause of COPD, but community air pollution and occupational exposure to dust, particularly among smokers, also contribute to COPD [Becklake 1992].

3.5.1.2 Epidemiologic Studies

Although thousands of studies have been published about occupational exposure to nonorganic dusts and COPD, only 13 studies of 4 cohorts of silica-exposed workers met rigorous methodologic criteria for a review conducted by Oxman et al. [1993]. Three of the cohorts were coal miners and one was South African gold miners. According to Oxman et al. [1993], the studies provided evidence that exposure to gold mine dust is an important cause of COPD, particularly in smokers, and that the risk of COPD appeared to be greater for gold miners than for coal miners.

3.5.2 Asthma

Crystalline silica has not been identified as an occupational asthma-inducing agent [Chan-Yeung 1994], and no published epidemiologic studies have specifically investigated whether asthma is related to crystalline silica dust exposure.

3.5.3 Chronic Bronchitis

3.5.3.1 Definition

Chronic bronchitis is clinically defined as the occurrence of chronic or recurrent bronchial hypersecretion (i.e., a productive cough) on most days of the week for at least 3 months of 2 sequential years [ATS 1987, 1995; Barnhart 1994]. The excess mucus secretion should not be related to a disease such as TB [ATS 1987, 1995]. Chronic bronchitis has been associated with both airflow obstruction and abnormalities in gas exchange [Barnhart 1994]. Although the terms "industrial bronchitis" and "occupational bronchitis" traditionally refer to chronic bronchitis that is associated with occupational exposure, bronchitic symptoms may also occur after occupational exposures that are acute or that last less than 2 years. An association between reduced ventilatory function and bronchitic symptoms has been reported in studies of workers exposed to coal dust, asbestos, or dust that contained crystalline silica [Barnhart 1994]. However, cigarette smoking is also associated with chronic bronchitis and must be considered when investigating the relationship between occupational exposures and bronchitic symptoms [Barnhart 1994; ATS 1997].

3.5.3.2 Epidemiologic Studies

Statistically significant ($P<0.05$) relationships independent of smoking were found between exposure[‡] to gold mine dust and chronic bronchitis or chronic sputum production in cross-sectional studies of gold miners in South Africa [Wiles and Faure 1977; Cowie and Mabena 1991] and Australia [Holman et al. 1987]. However, no statistically significant relationships independent of smoking were found between exposure and chronic bronchitis or bronchitic symptoms in cross-sectional studies of molybdenum miners [Kreiss et al. 1989b], uranium miners [Samet et al. 1984], taconite miners [Clark et al. 1980], Indian agate grinders and chippers [Rastogi et al. 1991], and a population-based study of South African gold miners [Sluis-Cremer et al. 1967] (Table 16).

Wiles and Hnizdo [1991] studied the relationship between mortality, airflow obstruction, and mucus hypersecretion in 2,065 South African gold miners. They found that after standardization for airways obstruction, mucus hypersecretion was not related to mortality from COPD (54 deaths). However, mucus hypersecretion remained significantly related to mortality from ischemic heart disease and all causes of death, even after adjustment for years of cigarette smoking and particle-years of exposure to gold mine dust [Wiles and Hnizdo 1991].

[‡]Cumulative exposure, duration of exposure, or intensity of exposure.

Table 16. Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Clark et al. [1980], United States	Cross-sectional study of bronchitic symptoms in 249 white male taconite miners; mean age was 49 with ≥20 yr of exposure to taconite dust. Control group of 86 men with no history of exposure to taconite mine dust.	80 dust-exposed smokers with cough all day	24%	—‡	—	Yes	Note that subgroups represent bronchitic symptoms—not cases. 33 controls were employees of a school; however, occupations of the other controls were not reported. Occupational dust exposures to the control group may have contributed to the similar or higher prevalences of bronchitic symptoms in that group.
		52 dust-exposed nonsmokers with cough all day	1%	—	—		
		24 nondust-exposed nonsmokers with cough all day	1%	—	—		
		32 nondust-exposed smokers with cough all day	16%	—	—		
		80 dust-exposed smokers with phlegm all day	18%	—	—		
		24 nondust-exposed nonsmokers with phlegm all day	1%	—	—		
		32 nondust-exposed smokers with phlegm all day	37%	—	—		

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Cowie and Mabena [1991], South Africa	Cross-sectional study of 1,197 black, male underground gold miners aged 28–76 with 25.1 yr since first exposure (mean). 857 miners had chronic silicosis.	Miners with chronic sputum production and "high" dust exposure	—	1.8§	1.19–2.69	Yes	62% of miners who smoked and 45% of miners who never smoked had "chronic bronchitic symptom complex."
		Miners with 24 pack-yr of smoking exposure and chronic sputum production	—	3.7	2.62–5.23**		"High" and "low" dust exposure categories were based on qualitative assessments of underground mine dust exposure and occupation. Authors stated that bronchitic symptoms may also have been related to underground mining exposures other than respirable quartz dust.

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Holman et al. [1987], Australia	Cross-sectional study of 1,363 male, current gold miners (51% were underground miners) aged 20 to >60. 53% of the cohort worked underground 1–19 yr.	Total cohort	14%††	—	—	Yes	ORs were based on comparison with nonminers and were adjusted for effects of smoking and age.
		Miners with chronic bronchitis:					
		1–9 yr of underground gold mining	—	1.8	1.0–3.3		
		10–19 yr of underground gold mining	—	2.5	1.2–5.2		
		≥20 yr of underground gold mining	—	5.1	2.4–10.9		
Kreiss et al. [1989b], United States	Community-based cross-sectional study of 389 male residents of Leadville, CO. 281 (72.2%) of the sample had worked at the local molybdenum mine. Mean yr of exposure: 9.3. Mean age of cohort: 44.	Underground miners with >10 yr of employment:				Yes	ORs were based on comparison with residents having no history of occupational dust exposure.
		With chronic cough	—	0.84	0.37–1.90		
		With chronic phlegm	—	0.93	0.42–2.06		Nearly half (49%) of personal samples for quartz exposures among the miners exceeded the NIOSH REL of 0.05 mg/m^3 (total number of samples was not reported).

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Ng et al. [1992b], Singapore	Cross-sectional study of 85 granite quarry workers with "high" dust exposure and 154 quarry workers with "low" dust exposure (see comments); mean age was 42. Mean duration of employment was 13.7 yr. Comparison group of 148 male postal workers with no exposure to granite dust; mean age was 40.	Quarry workers with "high" dust exposure:				Yes	No quantitative exposure concentrations for dust or silica were reported: granite quarry rock drillers and rock crushers were assumed to have "high" silica exposure; and administrative workers, truck drivers, vehicle maintenance workers, and loader operators were assumed to have "low" silica exposure. Results were adjusted for effects of age.
		All (85)	9	—‡‡	—		
		Nonsmokers (34)	2	—§§	—		
		Ex-smokers (5)	—	—	—		
		Current smokers (46)	7	—§§	—		

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Rastogi et al. [1991], India	Cross-sectional study of 240 male and 102 female agate grinders and chippers, and 116 male and 33 female controls with nondusty occupations. The mean duration of exposure was 10 yr for males and 8.9 yr for females.	Chronic bronchitis: Male: Agate workers Controls Female: Agate workers Controls Acute bronchitis: Male: Agate workers Controls Female: Agate workers Controls	 3.75/100 4.58/100 0 9.1/100 9.1/100 5.17/100 9.8/100 0	 — — — — — — $P<0.05$ —	 — — — — — — — —	Yes	Association between dust exposure and chronic bronchitis may not have been detected because the control group included workers who may have occupational exposure to respirable silica dust (e.g., rickshaw-pullers and sweepers). High prevalence of tuberculosis in agate workers and controls may have masked an association for bronchitis.
Samet et al. [1984], United States	Cross-sectional study of 192 male, current underground uranium miners aged <40, 40–59, and ≥60. 145 miners (76%) mined ≥10 yr underground.	Miners with chronic cough: 10–19 yr of mining ≥20 yr of mining Miners with chronic phlegm: 10–19 yr of mining ≥20 yr of mining	 14.1/100*** 22.7/100*** 31.9/100*** 36.6/100***	 — — — —	 — — — —	Yes	Chronic cough and chronic phlegm were not associated with duration of silica exposure in multiple logistic regression analysis (results were not reported).

See footnotes at end of table.

(Continued)

Table 16 (Continued). Epidemiologic studies of bronchitis in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Bronchitis cases in subgroup*	Risk measure (OR†)	95% CI	Adjusted for smoking	Comments
Sluis-Cremer et al. [1967], South Africa	Community-based, cross-sectional study of chronic bronchitis in 827 male residents who were aged >35 and who lived in Carletonville, a South African town with four gold mines.	Residents w/chronic bronchitis: Dust-exposed: Smokers Nonsmokers Nondust-exposed: Smokers Nonsmokers and ex-smokers	 199/394 (51%) 22/168 (13%) 45/161 (28%) 7/104 (7%)	 — — — —	 — — — —	Yes	"Dust-exposed" was defined as self-reported occupational exposure in a "scheduled dusty area" of a mine. A significant difference existed between the prevalence of chronic bronchitis in dust-exposed smokers and nondust-exposed smokers ($P<0.01$). No significant difference existed between dust-exposed and nondust-exposed nonsmokers or ex-smokers.
Wiles and Faure [1977], South Africa	Cross-sectional study of chronic bronchitis in 2,209 underground gold miners (race not reported) aged 45–54 with ≥10 yr of employment. 653 were ex-miners for ≥1 yr.	138 miners in highest cumulative dust exposure group: Nonsmokers Ex-smokers Smokers	 2/14 (14%) 4/31 (13%) 47/93 (51%)	 — — —	 — — —	Yes	Prevalence of chronic bronchitis increased with increasing mean dust concentration ($P<0.001$) and with cumulative dust exposure in nonsmokers ($P<0.05$), ex-smokers ($P<0.05$), and smokers ($P<0.001$).

*Number of cases unless otherwise indicated.
†Abbreviations: CI=confidence interval; NIOSH=National Institute for Occupational Safety and Health; OR=odds ratio; REL=recommended exposure limit.
‡Dash indicates *not reported*.
§Compared with miners having "low" dust exposure.
**Compared with miners having 0 pack-yr.
††Estimated prevalence.
‡‡Risk measure was not reported, but $P<0.01$ compared with controls.
§§Risk measure was not reported, but $P>0.05$ compared with controls.
***Standardized to the overall distribution of cigarette smoking.

A mortality study of workers in "dusty trades" reported a statistically significant number of deaths from bronchitis when compared with mortality rates for other white males in the United States ($P<0.05$; 6 deaths observed; 0.8 deaths expected) [Amandus et al. 1991].

The discrepancies among the cross-sectional studies of bronchitis in quartz-exposed populations may be attributable to the presence or absence of concurrent exposures among the cohorts that have been studied [Kreiss et al. 1989b]. Particle size is another factor that may have affected the results. The dust in one work environment may have had a higher proportion of particles that were not of respirable size[§] compared with dust in another work environment. Larger-sized dust particles may be responsible for large-airways diseases such as chronic bronchitis, whereas respirable dust particles are responsible for lung parenchymal diseases such as silicosis [Morgan 1978]. In addition to physical size, the shape and density of inorganic dust particles also influence where they are deposited in the airways and whether they can be cleared from the airways [Becklake 1985].

3.5.4 Abnormalities in Pulmonary Function Tests

3.5.4.1 Definition

Pulmonary function tests measure lung volumes (e.g., vital capacity [VC]), air flow (e.g., expiratory volume in 1 second [FEV_1]), blood gas exchange, and other aspects of lung function [Rosenstock 1994]. Spirometric pulmonary function tests routinely performed are forced vital capacity (FVC), FEV_1, and VC [Parkes 1982]. Lung function tests alone cannot diagnose any particular disease [Parkes 1982]; however, they are an important part of the clinical evaluation of workers with occupational lung diseases. Nonoccupational factors (e.g., the subject's age, height, racial group, and smoking habit) as well as the quality and interpretation of the spirometric testing can influence pulmonary function test results [Parkes 1982; Rosenstock 1994; Crapo 1994]. In general, an FEV_1 loss of about 20 to 30 ml/year in nonsmokers or >60 ml/year in smokers [Crapo 1994] may suggest a decline greater than expected. Wagner [1994] suggests further clinical evaluation of workers with a 15% decrease from the baseline percentage of predicted value for FEV_1 or FVC (e.g., from 105% to 90% of the predicted FEV_1).

Loss of FEV_1 has been associated with an increased risk of death from various diseases, including COPD [Crapo 1994; Tockman and Comstock 1989; Anthonisen et al. 1986; Foxman et al. 1986]. Although pulmonary function tests can define and measure respiratory impairment, they are not a diagnostic tool for silicosis or a measure of silica exposure [Wagner 1997], because no single pattern of pulmonary function abnormality is associated with silica exposure or silicosis [Wagner 1997; Weill et al. 1994; ATS 1997].

3.5.4.2 Epidemiologic Studies—Quantitative Estimates of Dust-Related Loss of Lung Function

Most epidemiologic studies of pulmonary function and occupational exposure to respirable crystalline silica are cross-sectional studies that do not provide quantitative modeling of cumulative dust exposure. They report occupationally related annual declines in ventilatory function in workers with and without silicosis (i.e., gold and other hard-rock miners, iron ore miners, coal miners, talc miners, slate workers, and kaolin workers). Details of these studies are reported elsewhere [ATS 1997; Becklake

[§]Respirable particles have aerodynamic diameters less than approximately 10μm.

1985, 1992; Eisen et al. 1995; NIOSH 1995a; EPA 1996; Graham et al. 1994].

Thirteen studies with quantitative dust exposure data for four silica-exposed cohorts found statistically significant associations between loss of lung function (i.e., FEV_1, FVC) and cumulative respirable dust exposure in coal miners and South African gold miners [Oxman et al. 1993]. The study of gold miners [Hnizdo 1992] estimated that a 50-year-old, white South African gold miner (nonsmoker) who was exposed to gold mine dust (containing 0.09 mg/m^3 of crystalline silica) at an average respirable concentration of 0.3 mg/m^3 for 24 years would lose 236 ml of FEV_1 (95% CI= 134–337). This loss is equivalent to about half of the estimated loss of FEV_1 in a typical U. S. male (nonminer) who smoked one pack of cigarettes per day for 30 years (i.e., 552 ml [95% CI=461–644]) [Dockery et al. 1988; Hnizdo 1992]. The combined effects of respirable dust exposure and smoking on the loss of FEV_1 were additive [Hnizdo 1992].

Epidemiologic studies of Vermont granite workers provided quantitative predictions of FEV_1 loss based on cumulative past exposure to granite dust. As shown in Table 17, the predicted FEV_1 loss for Vermont granite workers is 3 to 4 ml per $mg/m^3 \cdot$ year for cumulative exposure to granite dust and 2.9 ml per $mg/m^3 \cdot$ year for cumulative exposure to quartz dust. This estimate represents a loss of about 6.5 ml of FEV_1 for a working lifetime (i.e., 45 years) of exposure to crystalline silica at the current NIOSH REL of 0.05 mg/m^3. However, the findings of Theriault et al. [1974b] were based on measurements that may have been inaccurate. In 1979, Graham et al. [1981] administered pulmonary function testing to about 73% (n=712) of the workers tested in 1974 and found small annual increases in FEV_1. These researchers concluded that "technical deficiencies in the previous studies led to exaggerated and erroneous estimates of loss." The significance of predicted losses can be compared with the annual estimated FEV_1 decline for a nonminer who smokes one pack of cigarettes per day (10 ml/year) [Xu et al. 1992] or with the approximate annual FEV_1 decrease in men over age 25 (25 to 30 ml/year) [Burrows 1986].

A cross-sectional study of 389 male residents of a U.S. hardrock mining community also predicted FEV_1 loss [Kreiss et al. 1989b]. Multiple regression analyses found a significant difference ($P \leq 0.05$) in the mean FEV_1 for nonsmokers with dust exposure (96% of predicted FEV_1) compared with that of nonsmokers without occupational dust exposure (101% of predicted FEV_1) [Kreiss et al. 1989b].

3.5.5 Emphysema

3.5.5.1 Definition

Emphysema is the abnormal enlargement of the air spaces distal to the terminal bronchiole with destructive changes in the alveolar walls [ATS 1987]. Obvious fibrosis is not present [ATS 1987, 1995; Barnhart 1994; Becklake 1992], although small emphysematous spaces are frequently seen radiographically around the edges of large silicotic masses [Weill et al. 1994]. The diagnosis of emphysema is defined by pathologic criteria, and more recently by the presence of avascular spaces on computed tomographic (CT) scans of the lung [Barnhart 1994; Hayhurst et al. 1984]. Clinical signs include hyperinflation on chest radiographs, increased total lung capacity, reduced FEV_1, reduced diffusing capacity for carbon monoxide (DLCO) [Barnhart 1994], and weight loss [Stulbarg and Zimmerman 1996]. Emphysema is caused mainly by destruction of the lung parenchyma from excess proteolytic enzymes. One cause of excess proteolytic enzymes and the premature development of emphysema is the rare homozygous deficiency of the protein α_1-antitrypsin [Laurell and Eriksson 1963; Stulbarg and Zimmerman 1996]. Excess

Table 17. Loss of lung function (FEV_1)* associated with cumulative exposure to respirable granite dust

Reference and country	Study design, cohort, and followup	Subgroup	Loss of FEV_1		Adjusted for smoking	Comments
			Observed (estimated ml/yr)	Predicted (ml per $mg/m^3 \cdot year$)		
Eisen et al. [1995], United States	Longitudinal study of 618 white male granite workers hired after 1940, aged 25–65; employed 14.7 yr (mean), and followed 1970–1974 for annual pulmonary function testing [Eisen et al. 1983]. Quartz content of dust was 11% [Hosey et al. 1957].	Nonsmokers Smokers Nonsilicotic nonsmokers	34–72 53–69 —	— — 4†	Yes	Significant dose-response ($P<0.05$) was observed in the "dropout" group but not in the "survivor" group or the total cohort [Eisen et al. 1983]. After 1940, granite dust concentrations in Vermont granite sheds were <10 million particles per cubic foot (mppcf), or a respirable silica concentration of about 0.075 mg/m^3 [Davis et al. 1983]. Predicted loss based on results of linear regression models.
Theriault et al. [1974b], United States	Cross-sectional study of 792 male, current granite shed workers aged 25–65. Quartz content of dust was 9% [Theriault 1974a].	Granite dust exposure Quartz dust exposure	1.6‡,§ 1.5**	3§ 2.9§	Yes	Predicted loss based on results of multiple regression analysis. Exposure-response relationship found between cumulative dust exposure and cumulative quartz exposure and loss of FEV_1.

*Forced expiratory volume in 1 second.
†In dropout group (i.e., subjects lost to followup). No predicted loss in survivor group.
‡Per dust-year (i.e., granite shed dust exposure of 0.52 mg/m^3 for 40 hr/week for 1 yr).
§Included silicotics.
**Per quartz-year (i.e., quartz dust exposure of 0.05 mg/m^3 for 40 hr/week for 1 yr).

proteolytic enzymes can also occur when there is excessive recruitment of polymorphonuclear leukocytes (e.g., from damage caused by cigarette smoke) [Stulbarg and Zimmerman 1996].

Emphysema is classified microscopically by type based on the distribution of enlarged airspaces and destruction. The main types of emphysema include centriacinar, focal, centrilobular, panacinar, distal acinar, and irregular (scar) [Barnhart 1994; Parkes 1994]. Focal and centrilobular emphysema are the types frequently associated with environmental and occupational exposures. Focal emphysema is associated with exposure to coal dust, and centrilobular emphysema is commonly found in the upper lobes of the lungs of cigarette smokers and others exposed to chronic irritants [Barnhart 1994]. However, findings from a study of postmortem lung examinations showed that panacinar or centriacinar were the predominant types of emphysema found in the lungs of white South African gold miners [Hnizdo et al. 1991].

3.5.5.2 Epidemiologic Studies

Studies of emphysema in silica-exposed workers (excluding coal miners) show conflicting results: it is not clear whether silica exposure is associated with emphysema in all exposed workers or mainly in silica-exposed workers who smoke. In these studies, researchers have investigated cohorts of South African gold miners, usually by combining historical data about occupational exposures and smoking with postmortem examination of the lungs. (Attending physicians in South Africa who know or suspect that their deceased patient was a miner are legally required to remove the cardiorespiratory organs and send them to the Medical Bureau for Occupational Diseases if permission is granted by the next-of-kin [Goldstein and Webster 1976]).

Of the five studies presented in Table 18, one found that a significant relationship ($P<0.05$) independent of smoking and silicosis existed between gold mine dust exposure[**] and emphysema [et al. 1987]. Two studies found no relationship between emphysema and years of mining [Chatgidakis 1963; Cowie et al. 1993]. A study of emphysema type in 1,553 miners with autopsy examinations found that centriacinar emphysema was more common in smokers, whereas panacinar emphysema was more common in nonsmokers; exposure to gold mine dust was related to both types. A miner who had worked 20 years in high-dust occupations was 3.5 times more likely (95% CI= 1.7–6.6) to have emphysema (i.e., an emphysema score ≥30%) at autopsy than a miner who did not have a dusty occupation. However, the authors stated that this result was likely to "be true of smoking miners only because there were only four nonsmokers with an emphysema score between 30% and 40%" [Hnizdo et al. 1991]. Later, a study of 242 miners who were lifelong nonsmokers found that the severity of emphysema at autopsy was not related to most recent lung function measurements or to years of gold mining, cumulative dust exposure, or parenchymal silicosis after adjustment for age at death [Hnizdo et al. 1994]. All of the studies but two [Becklake et al. 1987; Hnizdo et al. 1994] found that the presence of emphysema was significantly associated with silicosis.

3.5.6 Nonmalignant Respiratory Disease (NMRD) Mortality

Epidemiologic studies of silica-exposed workers [Checkoway et al. 1993, 1997; Chen et al. 1992; Cherry et al. 1998; Brown et al. 1986; Costello and Graham 1988; Costello et al. 1995;

[**]The number of shifts worked in mining occupations with high dust exposure.

Table 18. Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Becklake et al. [1987], South Africa	Unmatched case-control study of 44 autopsied white gold miners with emphysema ≥ grade 2.0 (i.e., moderate or marked emphysema) and 42 controls without emphysema. Miners and controls were aged 51–70 at death (1980–1981).	Miners who smoked 20 cigarettes/day before 1960	—†	30.3‡	7.0–141.0	Yes	The presence of emphysema at autopsy was not associated with the presence of silicosis.
		Miners aged 70 at death	—	26.8‡	2.0–327.0	No	Deaths during 1980–1981 may not be typical of deaths in the total cohort of South African gold miners.
		Miners who worked 20 yr in occupations with "high" dust exposure	—	12.7‡	3.0–52.0	No	
Chatgidakis [1963], South Africa	Prevalence study of 800 consecutive autopsies of white gold miners conducted between January 1957 and October 1962.	Miners with silicosis and emphysema	297	44.58§	—**	No	Degree of emphysema was not related to years of service. Pulmonary diffuse emphysema increased significantly with incidence and degree of silicosis and with age.

See footnotes at end of table.

(Continued)

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Cowie et al. [1993], South Africa	Random sample of 70 black underground gold miners selected for computed tomography lung examination from 1,197 participants in a cross-sectional study conducted in 1984–1985.	Miners by emphysema grade: Grade 0 (no evidence) Grade 1 (<25% of lung affected) Grade 2 (25%–50% of lung affected)	 22 38 10	 — — —	 — — —	Yes	Presence and grade of emphysema were associated with silicosis ($P<0.002$; $P=0.006$) and smoking ($P<0.02$; $P=0.01$) but were not associated with years of underground mining. Low agreement (i.e., 37/70) between computed tomographic and radiologic assessments of silicotic nodule profusion categories.

See footnotes at end of table.

(Continued)

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Hnizdo et al. [1991], South Africa	Retrospective cohort study of the relationship of emphysema with lung function changes in 1,553 white gold miners aged ≥40 with autopsy examination between 1974 and 1987 and panacinar, centriacinar, or a mixed type of emphysema.	Miners who worked 20 yr in occupations with "high" dust exposure up to age 45	—	3.5‡	1.7–6.6	Yes (in some analyses)	Logistic regression model showed significant association between • centriacinar emphysema and silicosis ($P<0.001$), • emphysema and years of employment in a high-dust occupation for miners who smoked, • age and emphysema, and • average number of cigarettes smoked/day and emphysema. Possible misclassification of emphysema type.

See footnotes at end of table.

(Continued)

Table 18 (Continued). Epidemiologic studies of emphysema in workers exposed to silica dust

Reference and country	Study design, cohort, and followup	Subgroup	Number of emphysema deaths or cases in subgroup	Risk measure	95% CI*	Adjusted for smoking	Comments
Hnizdo et al. [1994], South Africa	Retrospective cohort study of relationship of emphysema with lung function in 242 white gold miners who were life-long nonsmokers, were aged ≥45 at death, and had an autopsy examination during 1974–1990.	Nonsmoking miners with moderate emphysema	4	—	—	Yes (all study subjects were nonsmokers)	For nonsmokers, degree of emphysema at autopsy was not associated (i.e., $P>0.05$ in multiple regression model) with years of gold mining, cumulative dust exposure, parenchymal silicosis, or lung function impairment after adjusting for age at death.

*Abbreviations: CI=confidence interval; OR=odds ratio.
†Dash indicates *not reported*.
‡OR for emphysema ≥ grade 2 at autopsy.
§Chi-square value (comparing silicotic miners with emphysema to silicotic miners without emphysema).
**$P<0.00001$.

Costello 1983; Steenland and Brown 1995b; Steenland and Beaumont 1986; Thomas and Stewart 1987; Thomas 1990] and silicotics [Goldsmith et al. 1995; Brown et al. 1997; Rosenman et al. 1995] found significant increases in mortality from NMRD, a broad category that can include silicosis and other pneumoconioses, chronic bronchitis, emphysema, asthma, and other related respiratory conditions.

The studies of U.S. gold miners [Steenland and Brown 1995b], U.S. diatomaceous earth workers [Checkoway et al. 1993, 1997], silicotic men in Sweden and Denmark [Brown et al. 1997] and parts of the United States [Rosenman et al. 1995], and U.S. pottery workers [Thomas and Stewart 1987] reported mortality ratios (SMRs or PMRs) for some categories of NMRD. However, the other studies either did not report SMRs for categories of NMRD or did not separate silicosis deaths from other categories of NMRD, thus limiting any conclusion about the association of silica exposure with death from a specific COPD based on death certificate data.

Some studies have reported exposure-response trends for NMRD and silica exposure. The study of diatomaceous earth workers found a statistically significant exposure-response trend for cumulative exposure to respirable crystalline silica and NMRD mortality after adjustment for the effects of age, calendar year, duration of followup, and ethnicity (rate ratio=5.35 in the highest exposure stratum [$\geq$5.0 mg/m^3 · year]; 95% CI=2.23–12.80; 15-year exposure lag) [Checkoway et al. 1997]. Other studies found exposure-response trends for NMRD mortality and duration of employment [Costello et al. 1995; Thomas and Stewart 1987], years since first exposure [Thomas and Stewart 1987], or qualitative categories of silica exposure (*none*, *low*, and *high*) [Thomas and Stewart 1987].

3.6 Autoimmune and Chronic Renal Diseases

In this century, many published case reports have described various autoimmune disorders in workers or patients who were occupationally exposed to crystalline silica [Bramwell 1914; Erasmus 1957; Jones et al. 1976; Mehlhorn 1984; Mehlhorn et al. 1990a; de Bandt et al. 1991; Yanez Diaz et al. 1992; Pelmear et al. 1992; Caux et al. 1991; Cointrel et al. 1997; Yamamoto et al. 1994; Guseva 1991; Ebihara 1982; Agarwal et al. 1987; Koeger et al. 1991, 1992, 1995; Anandan et al. 1995; Sanchez-Roman et al. 1993; Aoki et al. 1988; Fukata et al. 1983, 1987; Muramatsu et al. 1989; Masuda 1981; Tokumaru et al. 1990; Perez Perez et al. 1986; Bernardini and Iannaccone 1982; Siebels et al. 1995; Suratt et al. 1977; Meyniel et al. 1981; Hatron et al. 1982; Masson et al. 1997; Özoran et al. 1997; Haustein 1998; Cledes et al. 1982; Mehlhorn and Gerlach 1990]. The most frequently reported autoimmune diseases were scleroderma, systemic lupus erythematosus (lupus), rheumatoid arthritis, autoimmune hemolytic anemia [Muramatsu et al. 1989], and dermatomyositis or dermatopolymyositis [Robbins 1974; Koeger et al. 1991]. Case reports have also described health effects such as the following that may be related to the immunologic abnormalities in patients with silicosis: chronic renal disease [Saita and Zavaglia 1951; Bolton et al. 1981; Giles et al. 1978; Pouthier et al. 1991; Neyer et al. 1994; Dracon et al. 1990; Sherson and Jorgensen 1989; Rispal et al. 1991; Osorio et al. 1987; Bonnin et al. 1987; Arnalich et al. 1989; Wilke et al. 1996; Banks et al. 1983; Hauglustaine et al. 1980; Slavin et al. 1985], ataxic sensory neuropathy [Tokumaru et al. 1990], chronic thyroiditis [Masuda 1981], hyperthyroidism (Graves' disease) [Koeger et al. 1996], monoclonal gammopathy [Fukata et al. 1983, 1987; Aoki et al. 1988], and polyarteritis nodosa [Arnalich et al. 1989].

In addition to these case reports, 13 post-1985 epidemiologic studies reported statistically significant numbers of excess cases or deaths from known autoimmune diseases or immunologic disorders (scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and sarcoidosis), chronic renal disease, and subclinical renal changes (Table 19). Epidemiologic studies found statistically significant associations between occupational exposure to crystalline silica dust and several renal diseases or effects, including end-stage renal disease morbidity [Steenland et al. 1990], morbidity from end-stage renal disease caused by glomerulonephritis [Calvert et al. 1997], chronic renal disease mortality [Steenland and Brown 1995b], Wegener's granulomatosis (systemic vasculitis often accompanied by glomerulonephritis) [Nuyts et al. 1995], and subclinical renal changes [Hotz et al. 1995; Boujemaa et al. 1994; Ng et al. 1992a, 1993].

The pathogenesis of glomerulonephritis and other renal effects in silica-exposed workers is not clear. Some case reports provide evidence of an immunologic injury by immune complex formation, and other reports point to a direct toxic effect of silica [Calvert et al. 1997; Calvert and Steenland 1997; Kallenberg 1995; Wilke et al. 1996; Wilke 1997]. The immunologic aspects of renal disease are reviewed in Ambrus and Sridhar [1997].

The cellular mechanism that leads from silica exposure to autoimmune diseases is not known [Otsuki et al. 1998]. One theory is that when respirable silica particles are encapsulated by macrophages, fibrogenic proteins and growth factors are generated, and ultimately the immune system is activated [Haustein and Anderegg 1998; Ziegler and Haustein 1992; Haustein et al. 1992]. Immune activation by respirable crystalline silica may be linked to scleroderma, rheumatoid arthritis, polyarthritis, mixed connective tissue disease, systemic lupus erythematosus, Sjögren's syndrome, polymyositis, and fibrositis [Ziegler and Haustein 1992; Haustein et al. 1990; Otsuki et al. 1998]. A possible mechanism for development of scleroderma is a direct local effect of nonrespirable quartz particles that have penetrated the skin of workers [Green and Vallyathan 1996], as observed in skin samples from deceased scleroderma patients [Mehlhorn et al. 1990b].

In addition to the studies summarized in Table 19, there may be other epidemiologic data sets that have not been analyzed by methods that would detect a possible association between occupational exposure to crystalline silica and autoimmune diseases [Steenland and Goldsmith 1995]. Further clinical and immunologic studies are needed to characterize the relationship between occupational exposure to crystalline silica and autoimmune diseases.

3.7 Other Health Effects

Extrapulmonary deposits of silica have been reported. A review of the literature [Slavin et al. 1985] indicates that silica particles may be transported from the lungs and tracheobronchial lymph nodes to the spleen, liver, kidneys [Osorio et al. 1987], bone marrow, and extrathoracic lymph nodes as a result of (1) formation of silicotic lesions in pulmonary veins, (2) erosion of silicotic hilar nodules into pulmonary veins, and (3) rupture of silicotic nodules into the lymphatic system. Roperto et al. [1995] reported two cases of extrapulmonary silicosis in two water buffaloes that lived on a farm near a quartz quarry. Silicotic lesions were observed in the mesenteric lymph nodes, tonsils, and spleen. In humans with occupational exposure to silica, peritoneal silicosis has been misdiagnosed as pancreatic carcinoma [Tschopp et al. 1992] or abdominal malignancy [Miranda et al. 1996].

Intravenous injections of silica into the tail veins of rats have resulted in large liver

Table 19. Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Boujemaa et al. [1994], Belgium	Cross-sectional case-control study of 116 silicotic, male underground miners with no history of diabetes, nephrolithiasis, or hypertension and 61 age-matched controls from the general population. Urine samples were tested for albumin, retinol-binding protein, and NAG. Serum samples were tested for creatinine and β_2-microglobulin.	Silicotics	116	—†	—	Miners were examined an average of 23 yr after cessation of exposure. Mean duration of exposure was 14.9 yr. Duration of exposure and severity of silicosis were not associated with the measures of renal dysfunction. Silicotic miners had significantly higher urinary concentrations of albumin (P=0.017), retinol-binding protein (P=0.0045), and NAG (P=0.0001). Results were similar to those found by Hotz et al. [1995].

See footnotes at end of table.

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Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Bovenzi et al. [1995], Italy	Case-control study of 527 patients admitted to all hospitals in Trento province 1976–1991 and discharged with diagnosis of musculoskeletal disorder or connective tissue disease. Each scleroderma case was matched by age and gender to two controls who were without the disease under study and were from the same database.	Patients discharged with diagnosis of systemic sclerosis (according to specific diagnostic criteria):				—
		Women	16	0‡	—	
		Men	5	5.20§	0.48–74.1	

See footnotes at end of table.

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Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Burns et al. [1996], United States	Population-based case-control study of 274 women with confirmed systemic sclerosis diagnosed in Michigan between 1985 and 1991 and 1,184 female controls matched by race, age, and geographic region.	Women with self-reported exposure to the following:				Adjusted for age, race, and date of birth. Systemic sclerosis was not associated with self-reported exposures to silica dust or silicone (including breast implants).
		Abrasive grinding or sandblasting	3	0.34	0.10–1.10	
		Sculpting or pottery making	20	1.53	0.89–2.65	Same study design was applied to Ohio women with systemic sclerosis, and results were published later in a letter [Lacey et al. 1997].
		Working in a dental laboratory	3	1.52	0.44–5.26	
		Working with or near silica dust, sand, or other silica products	12	1.50	0.76–2.93	
Calvert et al. [1997], United States	Cohort morbidity study of 2,412 white, male underground gold miners employed ≥1 yr between 1940 and 1965 and alive on January 1, 1977.	Miners with cases of treated end-stage renal disease	11	1.37**	0.68–2.46	First epidemiologic study to examine incidence of end-stage renal disease in an occupational cohort.
		Nonsystemic††	6	4.22**	1.54–9.19	
		Systemic	4	0.80**	0.22–2.06	
		Unknown	1	1.54**	0.04–8.57	Subcohort of gold miners studied by Steenland and Brown [1995b].
						Mean respirable silica dust exposure of this subcohort was 0.05 mg/m^3.

See footnotes at end of table.

(Continued)

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Cowie [1987], South Africa	Cohort study of incidence of scleroderma in black gold miners seen by the medical service from July 1981 to June 1986.	Miners with scleroderma that met diagnostic criteria	10	81.8‡‡	—	—
Hotz et al. [1995], Belgium	Cross-sectional case-control study of prevalence of subclinical renal effects in 86 quarry workers employed 11 to 20 months with no clinical, spirometric, or radiographic signs of silicosis. Controls were manual workers [Bernard et al. 1994] matched by smoking status, body mass index, and age. Urine samples were tested for albumin, transferrin, creatinine, β_2-microglobulin, retinol-binding protein, silicon, and NAG. Serum samples were tested for creatinine and β_2-microglobulin.	—	86	—	—	Same cohort studied by Bernard et al. [1994]. Quarry workers had significantly higher urinary concentrations of albumin ($P<0.0004$), transferrin ($P<0.03$), retinol-binding protein ($P<0.001$), NAG ($P<0.001$), and silicon ($P<0.0001$). Controls may have been exposed to silica dust—occupational history of controls was not reported. Narrow range of employment duration may have limited the assessment of effects.

See footnotes at end of table.

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Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Klockars et al. [1987], Finland	Cohort morbidity study of 1,026 granite workers hired between 1940 and 1971 with followup until the end of 1981 for (1) incidence of disability pension awards for rheumatoid arthritis during 1969–1981, (2) prevalence of rheumatoid arthritis on December 31, 1981, and (3) prevalence of subjects receiving free medication for rheumatoid arthritis at the end of 1981. Referent group was composed of Finnish males.	Granite workers: Awarded disability pensions for rheumatoid arthritis	17§§	5.08***	3.31–7.79	Mean quartz concentrations measured in the granite quarries, processing yards, and crushing plants in 1970–1972 ranged from 0.02 to 4.9 mg/m^3.
		Receiving pensions for rheumatoid arthritis at end of study period	10§§	—	—	1.6 recipients expected (P<0.001).
		Receiving free medication for rheumatoid arthritis at end of study period	19†††	—	—	7.5 recipients expected (P<0.001).

See footnotes at end of table.

(Continued)

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Ng et al. [1993], Singapore	Cross-sectional study of subclinical renal effects in 67 granite quarry workers with no history of glomerulonephritis, urinary calculi, renal disease, diabetes, hypertension, or regular ingestion of analgesics. Workers' urine samples were tested for indicators of glomerular and tubular functions (i.e., albumin, AMG, BMG, and NAG).	Workers with low-dust-exposure jobs and no radiographic evidence of silicosis	31	—	—	Workers in the high-exposure group with ≥10 yr of employment had significantly greater ($P<0.05$) urinary concentrations of AMG, BMG, and NAG compared with workers in the low-exposure group. Quantitative dust exposure data not available. Preliminary findings were reported in Ng et al. [1992a]. Further studies are needed to define the clinical significance of AMG, BMG, and NAG as indicators of renal dysfunction in silica-exposed workers.
		Workers with high-dust-exposure jobs and <10 yr of employment	17	—	—	
		Workers with high-dust-exposure jobs and ≥10 yr of employment	19	—	—	

See footnotes at end of table.

(Continued)

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Nuyts et al. [1995], Belgium	Case-control study of occupational exposures of 16 patients diagnosed with Wegener's granulomatosis at six Belgian renal units between June 1991 and June 1993. Each patient was matched (by age, sex, and region of residence) with two controls randomly selected from lists of voters.	Patients with Wegener's granulomatosis (renal involvement) and reported occupational exposure to silica	5	5.0	1.4–11.6	Study had small sample size and was not designed specifically to examine exposure-response relationship of Wegener's granulomatosis with occupational exposure to silica. Further study is needed.
Rafnsson et al. [1998], Iceland	Population-based case-control study of residents in a district with a diatomaceous earth processing plant. Population included 8 sarcoidosis patients who were linked to a file of all past and present workers employed at the plant after it opened in 1967. 70 controls were randomly selected from the district population.	Sarcoidosis patients with occupational exposure to diatomaceous earth and cristobalite at the community plant	6	13.2	2.0–140.9	No matching of cases with controls. Mean values of personal samples of respirable cristobalite dust taken in 1978 and 1981 ranged from 0.002 to 0.6 mg/m^3. Stratification by number of hr worked (≥1,000 hr or <1,000 hr) indicated a dose-response trend. Further study of sarcoidosis and silica exposure is needed.

See footnotes at end of table.

(Continued)

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Rosenman and Zhu [1995]	Cohort morbidity study of men and women aged ≥20 and discharged from Michigan hospitals 1990–1991.	Patients with silicosis and rheumatoid arthritis:				No patients had silicosis and scleroderma.
		Women	0	—	—	
		Men	3	3.2**	1.1–9.4	
Sluis-Cremer et al. [1985], South Africa	Case-control study of silicosis in 79 white gold miners diagnosed with "definite" or "probable" progressive systemic sclerosis between 1955 and June 1984. Randomly selected control group of 79 miners in same patient index examined between May 1970 and April 1971; matched by age; without progressive systemic sclerosis.	—	79	1.18	0.26–5.38	Controlled for cumulative dust exposure. Although reported ORs suggested no association between silicosis and progressive systemic sclerosis, cases had higher cumulative dust exposure ($P<0.001$). This study was not designed to examine the possibility of a direct association between silica dust exposure and progressive systemic sclerosis.
Sluis-Cremer et al. [1986], South Africa	Case-control study of silicosis in 157 white gold miners diagnosed with "definite" or "probable" rheumatoid arthritis between 1967 and 1979. Each case was matched by age to a control subject without rheumatoid arthritis.	Miners with "definite" rheumatoid arthritis	91	3.79‡‡‡	1.72–8.36	Although the reported ORs suggested that gold miners with probable or definite rheumatoid arthritis were more likely to have silicosis as well, the study was not designed to examine the possibility of a direct association between silica exposure and rheumatoid arthritis. The results could not be explained by cumulative dust exposure or the intensity of exposure to gold mine dust.
		Miners with "probable" rheumatoid arthritis	66	1.94‡‡‡	0.81–4.63	

See footnotes at end of table.

(Continued)

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Steenland et al. [1990], United States	Population-based case-control study of occupational exposures of 325 men listed in the Michigan kidney registry and diagnosed with end-stage renal disease (excluding diabetic, congenital, and obstructive nephropathies) between 1976 and 1984. 325 controls matched by age, race, and area of residence.	Men with end-stage renal disease who reported occupational exposure to silica	87	1.67	1.02–2.74	Possible overreporting of exposure by cases.
Steenland et al. [1992], United States	Proportionate mortality study of 991 granite cutters who died after 1960 compared with causes of death in U.S. population.	Granite cutters: Arthritis deaths	17	2.01§§§	1.17–3.21	Study included all underlying and contributing causes of mortality after 1960 and other significant conditions that were documented on the death certificate.
		Chronic renal disease deaths (ICD–9 categories 582, 583, 585, 587)****	26	2.18§§§	1.43–3.20	

Table 19 (Continued). Epidemiologic studies of immunologic, autoimmune, and chronic renal disease (including subclinical renal changes) in silica-exposed workers

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure*	95% CI†	Comments
Steenland and Brown [1995b], United States	Mortality study of 3,328 white male gold miners employed underground ≥1 yr between 1940 and 1965 and followed for mortality from 1977 to 1990. Mortality rates of U.S. males used for comparison.	Arthritis (ICD–9 categories 711–716, 720–721) (see comments)	17	2.19††††	1.27–3.50	Study included all underlying and contributing causes of mortality after 1960 and other significant conditions documented on the death certificate.
		Other musculoskeletal disease as well as sclerosis, scleroderma, and lupus (ICD–9 categories 710, 717–719, 722–729, 731–739) (see comments)	10	2.14††††	1.03–3.94	Statistically significant exposure-response trend ($P<0.05$) for chronic renal disease mortality and cumulative dust exposure.
		Nonmalignant skin diseases (ICD–9 categories 690–709) (see comments)	10	2.45††††	1.17–4.51	
		Chronic renal disease in miners in highest cumulative dust exposure category (i.e., ≥48,000 dust-days)	8	2.77††††	1.20–5.47‡‡‡‡	

*Odds ratio unless otherwise indicated.
†Abbreviations: Dash indicates *not reported*; AMG=alpha-1-microglobulin; BMG=beta-2-microglobulin; CI=confidence interval; NAG=beta-n-acetyl-D-glucosaminidase; OR=odds ratio.
‡None exposed.
§For history of silica dust exposure.
**Standardized incidence ratio (SIR).
††That is, caused by glomerulonephritis or interstitial nephritis.
‡‡Incidence (cases) per million black gold miners. Incidence in general population of black men of similar age (33–57) was 3.4 cases per million ($P<0.001$).
§§Disability cases.
***Rate ratio.
†††Receiving arthritis medication through national insurance plan.
‡‡‡OR is for presence of silicosis.
§§§PMR.
****ICD–9 is the *International Classification of Diseases*, 9th Revision [WHO 1977].
††††SMR.
‡‡‡‡Reported in Steenland and Goldsmith [1995].

granulomas and hepatic silicosis [Kanta et al. 1986]. In workers exposed to crystalline silica, hepatic changes [Liu et al. 1991], hepatic or hepatosplenic silicosis [Clementsen et al. 1986; Oswald et al. 1995], and hepatocellular carcinoma [Clementsen et al. 1986] have been identified. Two studies reported a significantly higher proportion (P<0.05) of symptomatic hepatic porphyria (a chronic metabolic disease) in silica-exposed workers compared with control groups having no history of occupational silica exposure [Okrouhlílik and Hykeš 1983; Zoubek and Kordac 1986]. However, the effect of silica on porphyrin synthesis and metabolism is not clear. In one study, alcohol consumption (quantity not specified) may have been a confounder [Okrouhlílik and Hykeš 1983].

Mowry et al. [1991] reported a case of a cutaneous silica granuloma in a 57-year-old stonemason. Silica granulomas are firm, nontender dermal or subcutaneous nodules that usually appear at least several years (mean=10 years) after the exposure to silica. They may appear as a result of occupational exposure or trauma [Kuchemann and Holm 1979; Murphy et al. 1997] and are usually treated by excision. The mechanism that causes the silica crystals in the tissue to form a granuloma is unknown.

Cor pulmonale (enlargement of the right ventricle of the heart because of structural or functional abnormalities of the lungs) may occur as a complication of silicosis [Green and Vallyathan 1996] and other pneumoconioses [Kusiak et al. 1993a]. This condition is usually preceded by pulmonary arterial hypertension. An epidemiologic case-control study of 732 white South African autopsied gold miners reported a statistically significant association (P<0.05) of cor pulmonale with "extensive" and "slight" silicosis [Murray et al. 1993].

Pulmonary alveolar proteinosis is a rare respiratory disease identified by an accumulation of phospholipid material in the alveoli [McCunney and Godefroi 1989]. Cases of this disease were identified in a U.S. cement truck driver [McCunney and Godefroi 1989], a U.S. sandblaster [Abraham and McEuen 1986], and a French ceramics worker [Roeslin et al. 1980]. Each worker had been potentially exposed to crystalline silica.

Skin absorption of crystalline and amorphous silica particles from soil, and subsequent obstructive lymphopathies related to the fibrogenic effects of the particles may be related to the development of nonfilarial tropical elephantiasis (podoconiosis) in the lower legs of residents of East Africa and certain volcanic areas [Frommel et al. 1993; Fyfe and Price 1985; Price and Henderson 1981].

Silica dust exposure may be associated with abrasion-related deterioration of dental health. Petersen and Henmar [1988] reported a 100% prevalence of dental abrasion in a group of 33 Danish granite workers. The authors recommended that dust concentrations be reduced, that workers wear face guards, and that dental abrasion from occupational dust exposure be considered an occupational disease.

4 Experimental Studies

This section provides an abbreviated review of various experimental research studies. The reader is encouraged to consult the cited materials for complete information.

4.1 Biomarkers

A biomarker can indicate (1) the occurrence of exposure, (2) the effects of exposure, (3) the presence of early or frank disease, or (4) the susceptibility to disease or early effects of exposure [Committee on Biological Markers of the National Research Council 1987; Schulte 1995]. Useful biomarkers require (1) a definitive, validated link with the exposure or the risk of disease and (2) evidence of a dose-response relationship between the marker and the exposure [Schulte 1995]. The relationship between respirable silica dust exposure and silicosis is well established. However, the complex chain of cellular responses that leads to fibrosis and silicosis has not been fully discovered. The usefulness of biomarkers as a screening tool for silicosis risk will be realized when biomarkers in the chain of complex cellular responses are validated for their relationship to disease. In addition, the studies of blood, serum, sputum, bronchoalveolar lavage samples, and gene patterns of silica-exposed workers or silicotics (Table 20) are inconclusive for the following reasons:

1. The numbers of subjects are small, and few studies of similar markers exist for comparison.

2. The studies lack control for factors other than silica exposure that could change immunoglobulin concentrations.

3. The studies lack information about control groups, diagnostic criteria for silicosis, and baseline levels of markers.

4. Study results are inconsistent.

Further research on biomarkers in silica-exposed workers is needed to do the following:

1. Quantify the exact amount of soluble products in bronchoalveolar lavage in individual patients to provide more information about the mechanisms of fibrogenesis [Sweeney and Brain 1996]

2. Determine whether silicosis or silica-related lung cancers are associated with a specific gene or gene pattern

3. Determine whether a relationship exists between changes in immunoglobulin concentrations and silica exposure

4. Determine whether a dose-response relationship exists between changes in certain cellular components (lymphocytes and Clara cell protein) and silica exposure

Detailed reviews of the immunologic response to silica and other mineral dusts are available elsewhere (i.e., Heppleston [1994]; Haslam [1994]; Weill et al. [1994]; Davis [1991,1996]; Kane [1996]; Driscoll [1996]; Sweeney and Brain [1996]; Hook and Viviano [1996]; Gu and Ong [1996]; Iyer and Holian [1996]; Weissman et al. [1996]; Mossman and Churg [1998]).

Table 20. Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Bernard et al. [1994], Belgium	Belgium quarry workers who had worked <2 yr. Controls were manual workers without silica dust exposure, matched by smoking status, body mass index, and age.	86 quarry workers and 86 controls	Serum and sputum Clara cell protein (Clara cell 16)	Decreased concentrations of serum and sputum Clara cell protein in quarry workers (P=0.04) compared with controls.	Controls may have been exposed to silica dust. Short duration of exposure among quarry workers may have limited the analysis. Authors state that serum Clara cell 16 may be marker for toxic effects of silica particles on respiratory epithelium.
Borm et al. [1986], Netherlands	Male silicosis patients at a hospital in the Netherlands; exposed to silica for 10–38 yr. Controls were "healthy male, Caucasian blood donors" aged 50–65.	20 silicosis patients (15 coal miners, 4 ceramics workers, 1 foundry worker); 48 controls	Blood and plasma concentrations of hemoglobin, reduced and oxidized glutathione, glutathione peroxidase, and superoxide dismutase	Silicosis patients had significantly higher concentrations of red blood cell glutathione (P<0.0001).	Small number of subjects. Controls were not interviewed for their occupational history, and definition of "healthy" was not reported. Medication administered to patients may have been a confounder.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Brandt-Rauf et al. [1992], Finland	Prospective study of compensated pneumoconiosis patients; 91 blood samples were collected between 1983 and 1987. Cancer cases were identified in the Finnish Cancer Registry. 4 silicotics had worked as stone workers, 1 as a stone crusher, 2 as miners, and 3 as foundry workers. 3 silicotics with lung cancer were matched by age and smoking habits with 7 controls without cancer.	46 patients: 36 with asbestosis and 10 with ILO† category ≥1/1 silicosis	9 serum oncogene-related proteins or growth factors: growth factor PDGF-B (*sis*), TGF-β_1, *ras*, *fes, myb*, *int-1, mos, src, myc*	7/15 asbestosis patients had *ras* (p21) oncogene, but no oncogene-related proteins were found in the 10 silicosis patients. All silicosis patients had PDGF-B (*sis*) growth factor; only 42% of asbestosis patients had PDGF-B (*sis*).	Prospective study found that 3 of the 10 silicosis patients developed cancer during the study period (1983–1987). 2 patients had bladder cancer and 1 had lung cancer. PDGF may be a possible marker for development of severe or progressive silicosis. Study results suggest different pathogeneses for silicosis and asbestosis.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Calhoun et al. [1986], United States	Healthy, male, employed granite workers (non-smokers) with no clinical or radiographic evidence of silicosis. Volunteer controls of similar age and smoking history with no history of occupational exposure to dust. All workers and controls had BAL.	9 workers and 9 controls	IgG, IgM, IgA, albumin, and total protein (all were measured in BAL fluid and serum)	No significant differences in mean serum concentrations between workers and controls. Statistically significant differences (i.e., higher concentration) between IgG, IgA, IgM concentrations and lymphocyte counts in lavage fluid of workers compared with controls.	Authors concluded that inhalation of granite dust might initiate and sustain an immune-inflammatory response.
Gáliková [1982], Slovakia	Miners, drillers, and tunnelers, half with silicosis, aged 43–81, exposed 2–30 yr. Control group of healthy blood donors aged 42–82 with no history of exposure to inorganic dusts.	40 workers and 40 controls	Serum IgG, IgM,and IgA	No difference in IgM concentration. Significantly elevated average concentration of IgG in workers compared with controls ($P<0.001$). Significantly elevated average concentration of IgA in workers compared with controls ($P<0.05$). No significant differences in IgG, IgM, or IgA between silicotic and non-silicotic workers.	Method of silicosis diagnosis not reported.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Gualde et al. [1977], France	Caucasian silicosis patients (radiographic diagnosis) who had a silica-related occupation for 10–40 yr (38 gold, wolfram, and uranium miners; 35 porcelain workers; 2 quarry workers). "Normal and healthy" Caucasian controls plus second control group of porcelain workers employed 20–40 yr but with no clinical or radiographic signs of silicosis.	75 patients, 160 controls in first group, and 46 in control group of porcelain workers	27 HLA antigens (serum)	Prevalence of B7 antigen was significantly less ($P<0.05$ before correction for multiple comparisons of tested antigens) than in healthy or silica-exposed controls. No other significant differences found between silicotics and controls.	Small number of controls may have resulted in low statistical power to detect any differences after correction for multiple comparisons. Authors suggested that presence of B7 antigen may be related to resistance to development of silicosis. (See also Sluis-Cremer and Maier [1984] later in table.)
Honda et al. [1993], Japan	Japanese silicosis patients who had been sandblasters and who had radiographic evidence of silicosis. Controls were "healthy unrelated Japanese."	46 patients, 315 controls for HLA typing, and 94, 127, 100, or 128 controls for other analyses	HLA-DQ alleles, RFLP patterns, and IGLV gene extracted from peripheral granulocytes (medium not reported)	Some HLA-DQ alleles were more frequent in silicosis patients ($P<0.05$). RFLP pattern of C4A3–C4B5 allotype and IGLV more frequent in silicosis patients ($P<0.05$).	Source and occupational history of control group not reported. Definition of "healthy" not reported. Potential confounders of exposure and immunological outcomes not reported. Authors suggested that their findings indicate that a gene for silicosis may be near the HLA-B locus. Validation of these findings is needed.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Husgafvel-Pursiainen et al. [1997], Finland	Finnish white males with lung cancer (see comments).	5 patients with silicosis and 16 patients with asbestosis	Mutation of p53 gene and serum elevation of p53 protein (serum samples were not available for the silicosis patients)	Two of the five silicosis patients had lung tumors with DNA mutations of the p53 gene.	Subjects for study were drawn from cohort studied by Brandt-Rauf et al. [1992] (described earlier). The results of the serum tests do not support use of p53 assay by itself as a screening tool for lung cancer because only 36% of cancer cases tested positive for the mutant protein. The authors state that it may be a useful biomarker if combined with serum assays for altered oncoproteins as in the study by Brandt-Rauf [1992].
Karnik et al. [1990], India	Male slate pencil workers. Controls with no history of occupational exposure to dust or silica.	130 silica-exposed workers: 80 with ILO category 1, 2, or 3 silicosis and 50 controls	Serum IgG, IgM, and IgA	Higher concentrations ($P<0.05$) of IgG, IgM, and IgA in silicotic workers compared with controls.	Results may have been confounded by bacterial infections in some workers. Authors stated that an increase in immunoglobulin concentrations was not a marker for severity of silicosis.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Koskinen et al. [1983], Finland	Finnish male silicosis patients (ILO category ≥1/1) who had been exposed to silica dust ≥10 yr. Non-silicotic controls matched by age (±5 yr), duration of silica exposure (± 5 yr), and work environment. Additional control group of healthy Finnish blood donors.	27 patients; 27 non-silicotic, silica-exposed controls; and 900 blood donor controls	Serum HLA antigens	Higher prevalence of HLA-Aw19 in silicotics compared with non-silicotic, silica-exposed controls (P=0.02). Higher prevalence of HLA-Aw19 in unexposed blood donor group than in silica-exposed controls (P=0.04).	Authors state HLA-Aw19 may be marker for silicosis progression in Finnish population, but larger study groups are needed.
Kreiss et al. [1989a], United States	Silicotic residents from hardrock mining town in Colorado who had mined for 5–58 yr and were aged 30–59 when diagnosed with ILO category ≥1/0 silicosis. Published antigen prevalences of North American whites and international whites used for comparison.	49 silicotics, 1,029 North American controls, and 1,061–1,082 international controls	HLA-A, HLA-B, HLA-DR, and HLA-DQ antigens (blood)	Significantly higher prevalence of A29 and B44 in silicotics compared with two control groups (P<0.05 after correction for num-ber of antigens tested).	Population-based study design. A29 is a component of Aw19 (see Koskinen et al. [1983] above).

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Pevnitskiy et al. [1978], Russia	Male Russian patients aged 30–50 with "Stage I" silicosis who had been employed >10 yr in occupations with exposure to quartz dust (i.e., casting shop cleaners, sandblasters, and molders). Controls were "clinically healthy" Russian male blood donors aged 30–50.	32 silicosis patients and 32 controls	11 HLA antigens (6 on A locus and 5 on B locus) (serum)	Prevalence of HLA–B8 and HLA–B13 in silicotics was twice the prevalence in the control group (*P* value not reported).	Occupational history of control group not reported. Definition of "healthy" not reported. Definition of "Stage I" silicosis not reported. Small number of subjects and controls.
Sluis-Cremer and Maier [1984], South Africa	White South African gold miners who had been exposed to at least 20 "low-dust" years. Control group of Caucasian nonminers.	101 miners (45 silicotics of category ≥1/0 and 56 nonsilicotics) and 279 controls	29 HLA antigens (medium not reported)	Significantly fewer silicotics had B40 antigen compared with both silica-exposed and nonexposed comparison groups (P=0.02).	Source of control group not reported. No significant difference was found in the prevalence of B7, which does not agree with the findings of Gualde et al. [1977] (discussed earlier).
Sobti and Bhardwaj [1991], India	Male sandstone-crushing workers. Control group of local university teachers and students.	50 workers and 25 controls	Blood: SCE and CA	Higher proportion of SCE and CA in silica-exposed workers compared with controls (2.72% versus 1.28%; P<0.01). More SCEs (P<0.01) in smokers—both silica-exposed and nonexposed.	Dust contained 50%–60% crystalline silica, 14%–16% aluminum oxide, and 4%–5% iron oxide. Possible effect of socioeconomic differences between workers and control group not accounted for. No statistical test for correlation between duration of exposure and levels of SCE and CA. Silica exposure concentrations not reported.

See footnotes at end of table.

(Continued)

Table 20 (Continued). Molecular epidemiology studies of biomarkers for carcinogenesis or silicosis

Reference and country	Study design and cohort*	Number of subjects	Biologic marker	Results	Comments
Watanabe et al. [1987], Japan	Males aged 34–78, hospitalized with ILO category ≥2 silicosis and employed as tunnel workers or metal miners for a mean duration of 23.8 yr. "Normal" male controls aged 46–72 without silicosis.	82 patients and 25 controls	Total blood lymphocyte count and lymphocyte subsets: OKT3+, OKT4+, OKT8+, OKIa–1+ Serum IgG, IgM, IgA, IgD, and IgE	Silicosis patients with low lymphocyte counts (≤1,500 µl) had significantly increased IgG and IgA levels compared with controls (P<0.001). Decreased number of circulating T-cells in patients.	Source and occupational history of control group not reported. Definition of "normal" controls not reported. Potential confounders of exposure and immunological outcomes not reported. Need further study of relationship of silicosis with serum immunoglobulin levels and lymphocytes.

*Studies were cross-sectional unless otherwise indicated.

†Abbreviations: BAL = bronchoalveolar lavage; CA = chromosomal aberrations; HLA = human leukocyte antigen; Ig = immunoglobulin; IGLV = immunoglobulin lambda variable chain; ILO = International Labour Organization; PDGF = platelet-derived growth factor; RFLP = restriction fragment length polymorphism; SCE = sister chromatid exchange; TGF = transforming growth factor.

4.2 Cytotoxicity

Respirable crystalline silica is known to cause silicosis; however, the molecular mechanism responsible for the cellular injury that precedes the lung disease is unknown. Extensive in vitro and in vivo research has been conducted to evaluate the effects of crystalline silica on mammalian cells. Several mechanisms have been proposed to explain the cause of the cellular damage [Lapp and Castranova 1993]:

1. Direct cytotoxicity of crystalline silica

2. Stimulation of the alveolar macrophages by silica and subsequent release of cytotoxic enzymes or oxidants

3. Stimulation of the alveolar macrophages to release inflammatory factors (e.g., interleukin-8, leukotriene B_4, platelet-activating factor, tumor necrosis factor, platelet-derived growth factor) that recruit polymorphonuclear leukocytes, which in turn may release cytotoxins

4. Stimulation of the alveolar macrophages to release factors that initiate fibroblast production and collagen synthesis (e.g., interleukin-1, tumor necrosis factor, platelet-derived growth factor, fibronectin, and alveolar macrophage-derived growth factor)

4.3 Genotoxicity and Related Effects

Some studies have demonstrated the ability of quartz to induce micronuclei in mammalian cells in culture [Hesterberg et al. 1986; Nagalakshmi et al. 1995; Oshimura et al. 1984] (Table 21). However, other in vitro studies did not observe chromosomal aberration [Nagalakshmi et al. 1995; Oshimura et al. 1984], *hprt* (hypoxanthine-guanine phosphoribosyl transferase) gene mutation [Driscoll et al. 1997], or aneuploid or tetraploid cells [Price-Jones et al. 1980; Oshimura et al. 1984; Hesterberg et al. 1986]. An in vivo treatment of rats with quartz induced mutation in rat alveolar epithelial cells (Table 21) [Driscoll 1995; 1997].

Pairon et al. [1990] tested tridymite (i.e., Tridymite 118) and quartz (i.e., Min-U-Sil 5) particles for genotoxic effects. Tridymite induced a significant number of sister chromatid exchanges (SCEs) in co-cultures of human lymphocytes and monocytes ($P<0.05$ compared with control cells) at doses of 5 and 50 µg/cm^2 (87.9% of the tridymite particles had a diameter <1 µm). However, the number of SCEs in purified human lymphocytes that were treated with the same doses of tridymite particles did not differ significantly from control cells [Pairon et al. 1990]. Results of the same experiments with quartz did not yield a clear conclusion about the ability of quartz to induce a significant number of SCEs (Table 21) [Pairon et al. 1990].

In vitro cellular transformation systems model the in vivo process of carcinogenesis [Gao et al. 1997; Gu and Ong 1996]. The ability of quartz to induce dose-dependent morphological transformation of cells in vitro has been demonstrated in experiments with Syrian hamster embryo cells [Hesterberg and Barrett 1984] and mouse embryo BALB/c-3T3 cells [Saffiotti and Ahmed 1995]. Gu and Ong [1996] also reported a significant increase in the frequency of transformed foci of mouse embryo BALB/c-3T3 cells after treatment with Min-U-Sil-5 quartz. These studies indicate that crystalline silica can morphologically transform mammalian cells. However, further studies are needed to determine whether the transforming activity of silica is related to its carcinogenic potential.

Table 21. Summary of the genotoxic effects of quartz in mammalian cells

	In vitro studies		In vivo studies	
Genotoxic effect	Number of positive studies/number of studies available	Reference	Number of positive studies/number of studies available	Reference
Sister chromatid exchange	1*/3	Price-Jones et al. [1980] Pairon et al. [1990] (2 experiments)	1*/1	Sobti and Bhardwaj [1991]
Chromosomal aberrations	0/3	Nagalakshmi et al. [1995] (2 experiments) Oshimura et al. [1984]	1*/1	Sobti and Bhardwaj [1991]
Micronuclei	3/4	Oshimura et al. [1984] Hesterberg et al. [1986] Nagalakshmi et al. [1995] (2 experiments)†	0/1	Vanchugova et al. [1985]
Aneuploidy or tetraploidy	0/3	Price-Jones et al. [1980]; Oshimura et al. [1984]; Hesterberg et al. [1986]	0/0	
hprt mutation‡	0/1	Driscoll et al. [1997]	2/2§	Driscoll et al. [1995, 1997]

Source: IARC [1997].
*One questionably positive study available.
†One experiment by Nagalakshmi et al. [1995] showed an increase in the frequency of micronucleated cells at all concentrations tested, but the increase was statistically significant ($P<0.05$) only at the two highest concentrations tested.
‡*hprt* = hypoxanthine-guanine phosphoribosyl transferase.
§Mutagenic response associated with inflammation.

Researchers at the National Cancer Institute have examined the ability of quartz, cristobalite, and tridymite particles to cause deoxyribonucleic acid (DNA) damage (i.e., strand breakage) [Saffiotti et al. 1993; Shi et al. 1994; Daniel et al. 1993; Daniel 1993, 1995]. Although the results of those studies demonstrated the ability of crystalline silica to cause damage to isolated DNA in acellular systems, reviewers at IARC [1997] recently stated that the relevance of these assays to assess quartz-related genetic effects in vivo was "questionable" because (1) the nonphysiological experimental conditions did not apply to intracellular silica exposure and (2) very high doses of silica were used in the DNA breakage assays [IARC 1997].

Several studies conducted since the IARC review found that crystalline silica induced DNA damage (i.e., DNA migration). Zhong et al. [1997] found that by using the alkaline single cell gel/comet (SCG) assay, crystalline silica (Min-U-Sil 5) induced DNA damage in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblasts (Hel 299 cells) [Zhong et al. 1997]. Amorphous silica (Spherisorb), but not carbon black, was also found to induce DNA damage in these mammalian cells. However, the DNA-damaging activity of amorphous silica was not as high as the damaging activity of crystalline silica [Zhong et al. 1997]. Liu et al. [1996, 1998] challenged Chinese hamster lung fibroblasts with dusts pretreated with a phospholipid surfactant to simulate the condition of particles immediately after deposition on the pulmonary alveolar surface. Results of the experiments showed that untreated Min-U-Sil 5, Min-U-Sil 10, and noncrystalline silica induced micronucleus formation in a dose-dependent manner, but surfactant pretreatment suppressed that activity [Liu et al. 1996]. A subsequent experiment found that surfactant pretreatment suppressed quartz-induced DNA damage in lavaged rat pulmonary macrophages, but DNA-damaging activity was restored with time as the phospholipid surfactant was removed by intracellular digestion [Liu et al. 1998].

Shi et al. [1998] recently reviewed published literature on (1) the generation of reactive oxygen species (ROS) directly from silica and from silica-stimulated cells, (2) the role of ROS in silica-induced DNA damage and silica-induced cell proliferation, and (3) other silica-mediated reactions. A proposed mechanism for silica-induced generation of ROS species and carcinogenesis is described by Shi et al. [1998]. Experimental research is continuing to determine whether crystalline silica particles have a direct genotoxic effect that could cause lung tumor formation in humans.

4.4 Carcinogenicity

Experimental evidence of the carcinogenicity of quartz particles is based on the results of long-term inhalation and intratracheal instillation studies of rats, which are summarized in Tables 22 and 23 [Saffiotti et al. 1996]. Several issues are apparent from the results of the rat studies [Holland 1995]:

1. The appearance of tumors (usually adenocarcinomas or epidermoid carcinomas) is a late phenomenon.

2. Lung fibrosis is usually present in the rats with tumors.

3. No adequate dose-response data exist because multiple-dose experiments have not been conducted in the rat except for the inhalation study by Spiethoff et al. [1992].

4. Comparability of the intratracheal instillation and inhalation studies is difficult because of notable differences in methods and materials.

Table 22. Summary of data on lung tumors induced in rats by crystalline silica

Sample and exposure conditions	Rat strain	Sex	Incidence of lung tumors*		Reference	Comments
			Treated rats	Controls		
Quartz (Min-U-Sil 5):						
Intratracheal instillation of 7 mg/wk for 10 wk	Sprague-Dawley	—†	6/36	0/58	Holland et al. [1983]	Treated rats had 1 adenoma and 5 carcinomas.
Inhalation (nose only) of 12 ± 5 mg/m^3 for up to 2 yr	Fischer 344	F	20/60	0/54	Holland et al. [1986]	Treated rats had 6 adenomas, 11 adenocarcinomas, and 3 epidermoid carcinomas.
Inhalation of 51.6 mg/m^3 for various durations; sacrificed at 24 months	Fischer 344	F M	10/53 1/47	0/47 0/42	Dagle et al. [1986]	Treated female rats had 10 epidermoid carcinomas. Treated male rats had 1 epidermoid carcinoma.
Intratracheal instillation of 20 mg in left lung; sacrificed at 12, 18, or 22 months, or found dead	Fischer 344	M	30/67	1/75	Groth et al. [1986]	Treated rats had 30 adenocarcinomas. Controls had 1 adenocarcinoma.
Novaculite (i.e., microcrystalline quartz):						
Intratracheal instillation of 20 mg in left lung; sacrificed at 12, 18, or 22 months, or found dead	Fischer 344	M	21/72	1/75	Groth et al. [1986]	Treated rats had 20 adenocarcinomas and 1 epidermoid carcinoma. Controls had 1 adenocarcinoma.
Raw shale dust:						
Inhalation (nose only) of 152 ± 51 mg/m^3 (average quartz content: 8%–12%)	Fischer 344	F	17/59	0/54 1/15‡	Holland et al. [1986]	Treated rats had 2 adenomas, 8 adenocarcinomas, and 7 epidermoid carcinomas. Controls had 1 adenoma.

See footnotes at end of table.

(Continued)

Table 22 (Continued). Summary of data on lung tumors induced in rats by crystalline silica

Sample and exposure conditions	Rat strain	Sex	Incidence of lung tumors* Treated rats	Incidence of lung tumors* Controls	Reference	Comments
Spent shale dust:						
Inhalation (nose only) of 176 ± 75 mg/m^3 (average quartz content: 8%–12%)	Fischer 344	F	11/59	0/54 1/15‡	Holland et al. [1986]	Treated rats had 2 adenomas, 8 adenocarcinomas, and 1 epidermoid carcinoma. Controls had 1 adenoma.
Quartz (DQ12):						
Inhalation of 1 mg/m^3 for 24 months	Fischer 344	F	12/50	3/100 (male and female)	Muhle et al. [1989]	Treated female rats had 2 keratinizing cystic squamous cell tumors, 2 adenomas, and 8 adenocarcinomas. Treated male rats had 2 keratinizing cystic squamous cell tumors, 2 adenocarcinomas, 1 adenosquamous carcinoma, and 1 squamous cell carcinoma. Controls had 2 adenomas and 1 adenocarcinoma.
	Fischer 344	M	6/50	—		
Inhalation (nose only) of 6 mg/m^3 for 29 days followed by lifetime observation	Wistar	F	62/82	0/85	Spiethoff et al. [1992]	Treated rats had 8 adenomas, 17 bronchioloalveolar carcinomas, and 37 squamous cell carcinomas.
Inhalation (nose only) of 30 mg/m^3 for 29 days followed by lifetime observation	Wistar	F	69/82	0/85	Spiethoff et al. [1992]	Treated rats had 13 adenomas, 26 bronchioloalveolar carcinomas, and 30 squamous cell carcinomas.

Source: Adapted from Saffiotti et al. [1996].
*Number of lung tumors per number of rats observed.
†Not reported.
‡Investigators used two control groups.

Table 23. Lung tumors induced in Fischer 344 rats by a single intratracheal instillation of quartz

Treatment sample and dose*	Sex	Observation time	Incidence of lung tumors		Total number of lung tumors‡	Histological types
			Number†	%		
Untreated:						
No dose	M	Died after 17 months	0/32	—	0	—
No dose	F	Died after 17 months	1/20	5	1	1 adenoma
Quartz (Min-U-Sil 5):						
12-mg dose	M	Sacrificed at 11 months	3/18	17	37	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, and 3 epidermoid carcinomas
		Sacrificed at 17 months	6/19	32		
		Died after 17 months	12/14	86		
12-mg dose	F	Sacrificed at 11 months	8/19	42	59	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, and 3 epidermoid carcinomas
		Sacrificed at 17 months	10/17	59		
		Died after 17 months	8/9	89		
20-mg dose	F	Died after 17 months	6/8	75	13	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, and 1 epidermoid carcinoma
Quartz (hydrogen fluoride-etched Min-U-Sil 5):						
12-mg dose	M	Sacrificed at 11 months	2/18	11	20	5 adenomas, 14 adenocarcinomas, and 1 mixed carcinoma
		Sacrificed at 17 months	7/19	37		
		Died after 17 months	7/9	78		
12-mg dose	F	Sacrificed at 11 months	7/18	39	45	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, and 5 epidermoid carcinomas
		Sacrificed at 17 months	13/16	81		
		Died after 17 months	8/8	100		

Sources: Saffiotti et al. [1993; 1996].
*As mg quartz suspended in 0.3 ml saline.
†Number of rats with lung tumors per number of rats observed.
‡At all observation times.

Although new long-term carcinogenesis studies in animals may provide information about dose-response relationships and inhibition of quartz toxicity or reactivity in vivo, in vitro studies are needed to develop effective cellular and molecular models of carcinogenesis [Holland 1995; Saffiotti et al. 1996].

5 Conclusions

The following conclusions about the health effects caused by exposure to respirable crystalline silica are derived from studies in humans and animals published since the 1974 criteria document [NIOSH 1974]. These studies support the risk of silicosis, lung cancer, and several other debilitating and fatal diseases from occupational exposure to crystalline silica. The onset of silicosis and lung cancer is thought to be related to the biological activity and the lack of solubility of crystalline silica particles in body fluids and tissues.

5.1 Lung Cancer

In 1988 testimony to the U.S. Department of Labor, NIOSH recommended that respirable crystalline silica be considered a potential occupational carcinogen [54 Fed. Reg. 2521 (1989)]. Since then, additional studies have supported a lung cancer risk from exposure to crystalline silica:

- Lung cancer is associated with occupational exposures to crystalline silica [ATS 1997], specifically quartz and cristobalite [IARC 1997].
- An exposure-response relationship has been reported in studies of miners, diatomaceous earth workers, granite workers, pottery workers, refractory brick workers, and other workers (see Section 3.4.2).
- Meta-analyses of the epidemiologic studies of silica exposure and lung cancer reported a moderate summary relative risk of 1.3 for silica-exposed workers [Steenland and Stayner 1997] and higher summary relative risks of 2.2 to 2.8 for silicotic workers [Steenland and Stayner 1997; Tsuda et al. 1997; Smith et al. 1995]. Some of the studies of silica-exposed workers controlled for the effects of smoking and others did not. The available data also support the conclusion that silicosis produces an increased risk for bronchogenic carcinoma, but the data are "less clear" as to whether silica exposure is associated with lung cancer in the absence of silicosis [ATS 1997].

5.2 Noncarcinogenic Health Effects

In 1974, NIOSH established an REL for respirable crystalline silica of 0.05 mg/m^3 as a 10-hr TWA to prevent the risk of silicosis from occupational exposure [NIOSH 1974]. Since then, additional studies have indicated that a risk for silicosis exists at the NIOSH REL. Three recent epidemiologic studies have shown that the estimated risk of silicosis for a 45-year working lifetime is 47% to 90% for cumulative silica exposures at concentrations equal to the current OSHA and MSHA PELs, and approximately 10% to 30% at concentrations equal to the NIOSH REL (see appendix) [Kreiss and Zhen 1996; Steenland and Brown 1995a; Hnizdo and Sluis-Cremer 1993]. The results from these studies support the need for continued medical and epidemiologic surveillance of workers after they leave employment and for revision of OSHA and MSHA standards for respirable crystalline silica.

Additional studies have reported the risk for several other debilitating and fatal diseases:

- Several epidemiologic studies have reported statistically significant numbers of excess deaths or cases of immunologic disorders and autoimmune diseases in silica-exposed workers. These diseases and disorders include scleroderma [Steenland and Brown 1995b; Cowie 1987], rheumatoid arthritis [Sluis-Cremer et al. 1986; Klockars et al. 1987; Rosenman and Zhu 1995], systemic lupus erythematosus [Steenland and Brown 1995b], and sarcoidosis [Rafnsson et al. 1998].

- Recent epidemiologic studies have reported statistically significant associations of occupational exposure to crystalline silica with renal diseases and subclinical renal changes [Steenland et al. 1990, 1992; Steenland and Brown 1995b; Calvert et al. 1997; Nuyts et al. 1995; Hotz et al. 1995; Boujemaa et al. 1994; Ng et al. 1993].

- Crystalline silica may affect the immune system, leading to mycobacterial infections (tuberculous and nontuberculous) or fungal infections [ATS 1997; NIOSH 1992a,b, 1996b; Ziskind et al. 1976; Parkes 1982; Parker 1994], especially in workers with silicosis [Corbett et al. 1999; Kleinschmidt and Churchyard 1997; Althouse et al. 1995; Goldsmith et al. 1995; Hnizdo and Murray 1998; ATS 1997].

- Occupational exposure to respirable crystalline silica is associated with bronchitis, COPD, and emphysema (see Section 3.5). Some epidemiologic studies suggest that these health effects may be less frequent or absent in nonsmokers.

5.3 Exposures, Monitoring, and Controls

Published studies on workers exposed to crystalline silica indicate that exposures still occur at concentrations exceeding the OSHA and MSHA PELs and the NIOSH REL. Engineering control methods used to control silica exposures in some industrial environments may not be feasible for reducing airborne exposures in other workplaces where their implementation is hindered by the type of work being performed. In addition, sampling and analytical techniques used to measure airborne crystalline silica exposures are limited in their ability to accurately quantify exposures below the NIOSH REL. The following issues must be resolved to prevent silicosis and other debilitating and fatal diseases:

- Many occupational exposures to crystalline silica still exceed applicable Federal standards. Of the 255 industries targeted for OSHA inspection between 1980 and 1992, 48% had overall average exposures for respirable quartz that exceeded the PEL [Freeman and Grossman 1995]. Analysis of OSHA compliance data for five of the three-digit SICs (masonry and plastering, heavy construction, painting and paper hanging, iron and steel foundries, and metal services) for the period 1979–1995 indicated that an estimated number of workers were exposed to concentrations of respirable crystalline silica that were at least 10 times the NIOSH REL of 0.05 mg/m^3 (10-hr TWA) [Linch et al. 1998] (see Section 2.3).

- Workers are exposed to crystalline silica in a variety of industries and occupations in which engineering controls may not be feasible for reducing exposures and may necessitate the use of other worker protection measures such as substitution

(use of a less hazardous material) or respirator use.

- Current sampling and analytical methods used to evaluate occupational exposure to crystalline silica do not meet the appropriate accuracy criterion needed to quantify exposures at concentrations below the NIOSH REL of 0.05 mg/m^3 (see Section 2.4). However, the recent introduction of a new sampler that can operate at a higher flow rate and the ongoing improvements in the analysis of crystalline silica should soon make it possible to measure crystalline silica exposure accurately when it is below 0.05 mg/m^3.

Until these improved sampling and analytical methods are developed for respirable crystalline silica, NIOSH will continue to recommend an exposure limit of 0.05 mg/m^3 to reduce the risk of developing silicosis, lung cancer, and other adverse health effects. NIOSH also recommends minimizing the risk of illness that remains for workers exposed at the REL by substituting less hazardous materials for crystalline silica when feasible, by using appropriate respiratory protection when source controls cannot keep exposures below the NIOSH REL, and by making medical examinations available to exposed workers.

6 Research Needs

6.1 Health-Related Research

The relationship of occupational crystalline silica exposure with silicosis and other silica-related diseases is well documented in the literature. However, the mechanisms and particle characteristics that cause silicosis and other silica-related diseases have not been precisely defined. Prevention of silicosis, lung cancer, and other silica-related diseases can be facilitated by the following:

- Development of methods for earlier detection or more definitive noninvasive evaluation of silica-related pulmonary disease, such as methods to improve the sensitivity of radiography for detecting silicosis (these methods were reviewed by Wilt et al. [1998] and Talini et al. [1995])

- Further in vitro and in vivo studies of mechanisms for development of

  — silicotic nodules [Craighead 1996]

  — autoimmune diseases

  — DNA damage by silica particles [Saffiotti et al. 1994]

- Further in vitro and in vivo studies of the toxicity and pathogenicity of

  — alpha quartz compared with its polymorphs [Craighead 1996]

  — crystalline silica compared with crystalline glass, amorphous silicone, and silicates [Craighead 1996]

  — crystalline silica compared with substitute materials for abrasive blasting and other tasks that use crystalline silica

  — dust mixtures that contain crystalline silica [Craighead 1996; Donaldson and Borm 1998; Dufresne et al. 1998]

  — quartz contaminated with trace elements [Castranova et al. 1997]

- The association of surface properties of silica particles with specific work processes and health effects

- Cellular, molecular, and animal models of silica carcinogenesis to explore whether silica dust is an initiator or a promoter of lung cancer [Craighead 1996] and to evaluate a dose-response relationship

- Animal models of individual susceptibility and the development of fibrosis [Craighead 1996], including the translocation of silica particles from the lungs [Adamson and Prieditis 1998]

- Animal models of the adverse effects of crystalline silica on the kidneys and liver

- Routes and kinetics of lymphatic transport and deposition of silica particles [Craighead 1996]

Further epidemiologic studies and surveillance of silica-exposed workers are needed to do the following:

- Determine the exposure-response relationship between occupational silica dust exposure and lung cancer in nonsmokers
- Determine why lung cancer risks appear to be higher in silicotic workers (e.g., determine the histologic type and anatomic location of lung cancers in workers with and without silicosis [Ducatman et al. 1997])
- Evaluate exposure-response relationships between occupational silica dust exposure and (1) TB [ATS 1997] and (2) changes in cellular components (lymphocytes, Clara cell protein) or immunoglobulin concentrations
- Determine the relationship between occupational exposure to silica dust and
  - —TB in silica-exposed workers without diagnosed silicosis
  - —clinically significant changes in the lung function of nonsmokers
  - —emphysema in nonsmokers
  - —gastric cancer and other nonpulmonary cancers
- Gather uniform national and international prevalence and incidence data about silicosis cases to identify industries, occupations, and work areas where preventive measures could be implemented [CSTE 1996; Wagner 1997]
- Gather prevalence, incidence, and mortality data about silica-related diseases such as cancer, scleroderma and other autoimmune diseases, nonmalignant renal disease, and other adverse health effects to assess morbidity and mortality risk factors and to identify areas where preventive measures could be implemented
- Determine whether silicosis or silica-related lung cancers are related to a specific gene, gene pattern, or other individual susceptibility factors
- Improve the methods for estimating historical exposures for retrospective cohort studies
- Improve the assessment of potential confounding and synergistic effects of smoking in silica-exposed workers [Checkoway 1995]
- Improve the assessment of potential confounding and synergistic effects of other carcinogens present in the work environment of silica-exposed workers [Dufresne et al. 1998]
- Determine whether adverse health effects are associated with occupational exposure to materials that could be substitutes for crystalline silica [NIOSH 1992a]

6.2 Research Related to Exposure Measurement

Reducing the OSHA and MSHA PELs for crystalline silica to concentrations below the NIOSH REL (0.05 mg/m^3 for up to a 10-hr workday during a 40-hr workweek) would require new methods that can accurately measure low airborne concentrations at the NIOSH accuracy criterion. (Limitations of

current NIOSH methods for measuring worker exposure to airborne crystalline silica are discussed in Chapter 2). Such new methods will depend on the following types of research and development:

- Reevaluation of the 10-mm nylon cyclone, the GK2.69 cyclone, or other proposed devices at exposure concentrations below 0.05 mg/m^3
- Ascertainment of the sampling efficiency of proposed samplers versus particle aerodynamic diameter
- Side-by-side comparison of proposed samplers under field conditions
- Development of samplers that can operate at higher flow rates than those currently available
- Development of working standards that use different types of filter media (e.g., PVC) to reduce errors in calibration
- Further improvement of the system used to produce replicate crystalline silica samples for the PAT Program* to
  - improve the reproducibility of interlaboratory results for silica analysis,
  - eliminate problems with sample overloading, and
  - determine how to account for bias between results from different analytical methods
- Further research to validate the feasibility of "on-filter" analysis under field conditions (preliminary investigation of particle transition between the cyclone and the sample collection cassette indicates that it is possible to improve the uniformity of particles deposited on the filter to permit an accurate on-filter analysis)
- Collaborative testing of any improved or new sampling and analytical methods to demonstrate equivalence

*This system has undergone improvements from its original form to reduce the intersample variability. Currently, intersample CV is on the order of 0.08 to 0.12. Only cursory testing of these improvements has been carried out, and further improvements may be necessary.

6.3 Research Related to the Control of Exposure

Protecting workers from crystalline silica exposures can be accomplished through a number of means. Respiratory protection and administrative controls are important means of protecting workers, but they should not be used as the primary method of preventing worker exposure. Other exposure control methods (including process modifications to eliminate hazards, substitution, and engineering controls) should be the primary focus of any safety and health program in preventing occupational exposures. For some industries, research is needed to develop cost-effective controls; whereas in other industries, work is needed to increase the availability and use of control measures and to explore barriers that prevent the introduction of control technology. Specific types of research are needed in the following industries:

- *Construction*. The construction industry presents a major challenge for protecting workers. In this industry, crystalline silica is present in many of the building materials and construction substrates (i.e., rock and soil). Silica sand is a major component of concrete and mortar and is used in the production of brick

and concrete masonry units. In addition to the ubiquitous presence of silica in construction, this industry also faces a challenge from the ever-changing nature of the worksite. These changes create two problems in the control of silica exposures. First, permanent control measures are not feasible for many worksites because of the short duration of the task (e.g., concrete cutting or coring operations). Second, the manner in which the work is performed at a worksite can create a silica exposure for workers at adjacent worksites. Control methods such as wet cutting of bricks and concrete masonry units and use of high-velocity/low-volume (HVLV) ventilation systems during cutting and grinding of concrete have been effective in reducing exposures to silica at some worksites. However, the following research is needed to improve these techniques and the feasibility of their use:

- The use of water is not a feasible control method for reducing exposures on many interior jobs or in cold temperatures. Research is needed to find methods for increasing (1) the applicability of water to more operations and (2) the use of water in applications where it is considered feasible.

- The use of HVLV ventilation involves problems such as insufficient hood capture velocity, obstruction of the work area by the control, and poor dust collector performance. Research is needed to improve the performance of HVLV systems and the feasibility of their use in other operations.

- Alternative materials and work methods can be used to reduce crystalline silica exposures. For example, concrete forms can be used to impart smoother surface finishes and reduce the need for additional grinding or rework. Additional research is needed to investigate alternative methods for blowing and sweeping on construction sites (e.g., the use of vacuums instead of compressed-air lances to remove debris from cracks in road construction).

- *Foundries*. Foundries use large volumes of sand in the molds and the cores to produce castings. In general, foundries that cast higher-temperature metals (steel, gray iron, and stainless steel) have the potential for creating higher silica exposures than foundries that cast lower-temperature metals (aluminum, brass, and bronze). The molding sand used in most foundries contains a small percentage of water and other binders. High temperatures dry the sand, making it more likely to become airborne. Various types of controls are being used in foundries, but additional research is needed:

  - Alternative processes such as the lost foam casting process have been used for some metal castings, but they require additional investigation to determine whether they can effectively reduce exposures by minimizing the amount of casting cleaning and sand handling required to produce high-quality castings.

  - Industrial ventilation is widely used to capture and contain silica-containing aerosols. However, its effectiveness is only as good as its design, installation, and maintenance. Research is needed on methods for effectively communicating the need for routine

and proper maintenance of ventilation systems.

— Automated processes in foundries need to be explored so that workers can be removed from operations that generate high silica exposures.

— The use of HVLV ventilation systems during casting cleaning needs to be evaluated.

— Alternative methods should be investigated for blowing and sweeping in foundries. Vacuums may be feasible as an alternative to compressed-air lances and dry sweeping.

- *Abrasive blasting operations*. Abrasive blasting operations have been documented to generate some of the highest crystalline silica exposures. Other blasting materials such as steel shot, steel grit, and boiler slag have been used as substitutes for silica sand. However, additional research is needed to determine the safety of substitute blasting materials. In addition, replacing silica sand with a substitute blasting material will not eliminate silica exposures when blasting on silica substrates such as concrete or granite. Many of these operations may be modifiable to reduce the amount of blasting required. Additional research is needed on alternative blasting methods such as high-pressure water jetting, slurry blasting, and vacuum blasting. All of these may reduce exposures associated with silica-containing substrates.

- *Surface and other mining*. Technology exists in the surface mining industry to control exposure to crystalline silica. However, silicosis persists because controls are often not implemented or properly maintained [NIOSH 1996b]. Effective methods are needed for informing drillers and drill owners about the need for continued maintenance and proper use of dust controls on drills. Mine workers at other than surface sites have silica exposures that have not been well characterized. For example, little or no information is available about dust control measures for hard-rock tunneling operations. Research is needed to determine which control measures provide the best protection and are feasible to implement.

- *Paints, coatings, glass, cosmetics, plastics, and cleaning products*. Crystalline silica is used in a diverse number of products, including paints, coatings, glass, cosmetics, plastics, and cleaning products. However, the hazards associated with silica exposure are often not recognized in these industries. Research is needed to develop methods for communicating hazards and controls to workers and employers. The need is for innovative technologies that can be transferred across industries. Additional research is needed to investigate the feasibility of using HVLV ventilation systems and water to reduce exposures in these industries.

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Appendix
Occupational Exposure Limits

Table A–1. U.S. guidelines and limits for occupational exposure to crystalline silica

Reference	Substance	Guideline or limit (mg/m^3)
NIOSH [1974]	Crystalline silica:* quartz, cristobalite, and tridymite as respirable dust	REL† = 0.05 (for up to a 10-hr workday during a 40-hr workweek)
OSHA [29 CFR 1910.1000–Table Z-3]	Respirable crystalline silica, quartz	PEL = 10 ÷ % quartz + 2 (8-hr TWA)
	Respirable crystalline silica, cristobalite	PEL = half of the value calculated from the formula for quartz
	Respirable crystalline silica, tridymite	PEL = half of the value calculated from the formula for quartz
MSHA [30 CFR 56, 57, 70, 71]	Respirable quartz in underground and surface metal and nonmetal mines	PEL = 10 ÷ % quartz + 2 (8-hr TWA)
	Respirable crystalline silica present in concentrations >5% in surface and underground coal mines	RDS† = 10 ÷ % quartz (8-hr TWA)
ACGIH [2001]	Respirable crystalline silica, quartz	TLV = 0.05 (8-hr TWA)
	Respirable crystalline silica, cristobalite	TLV = 0.05 (8-hr TWA)
	Respirable crystalline silica, tridymite	TLV = 0.05 (8-hr TWA)

Adapted from Hearl [1996].
* Identified by NIOSH as a potential occupational carcinogen [54 Fed Reg. 2521 (1989)].
† Abbreviations: REL = recommended exposure limit; PEL = permissible exposure limit; RDS = respirable dust standard; TLV = threshold limit value; TWA = time-weighted average.