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Ambient Levels and Noncancer Health Effects of Inhaled Crystalline and Amorphous Silica:

Health Issue Assessment

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PREFACE

The National Center for Environmental Assessment has prepared this health assessment of silica to serve as an information source document for use by the U.S. Environmental Protection Agency (EPA).

In the development of this assessment document, the scientific literature through 1995 has been inventoried, key studies have been evaluated, and a summary and conclusions have been prepared so that the noncancer toxicity and related characteristics of amorphous and crystalline forms of silica are identified qualitatively. Information regarding sources, emissions, ambient air concentrations, and public exposure has been included to give the reader an indication of the levels of silica in the ambient air to which a population may be exposed. Although the available information is presented as accurately as possible, it is limited primarily to particulate matter measurements, and, to some extent, ambient silica level measurements are dependent on assumptions rather than on specific data. Appropriate and current information regarding silica-specific sources, emissions, and ambient air concentrations is needed to provide additional information for drawing health risk or regulatory conclusions regarding the extent and significance of public exposure to this substance.

Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the health effects is placed in perspective with observed environmental levels. Although this document does not constitute a formal EPA quantitative risk assessment, current issues relevant to a quantitative risk assessment of the noncancer health effects from crystalline silica exposure are reviewed. Further, this document is not a review of the potential carcinogenicity of silica, nor does it address extensively the more general effects of particulate matter exposures. Its primary focus is the noncancer silica-specific health effects literature.

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ABBREVIATIONS AND ACRONYMS

AP	Alkaline phosphatase
BAL	Bronchoalveolar lavage
BMD	Benchmark dose
CARB	California Air Resources Board
CAS	Chemical Abstract Service
CEI	California Emissions Inventory
CI	Confidence interval
CSE	Cumulative Silica Exposure
CT	Computerized tomogram
d_{ae}	Aerodynamic equivalent diameter
d_{ar}	Aerodynamic resistance diameter
DNA	Deoxyribonucleic acid
DRI	Desert Research Institute
EDXA	Energy dispersive X-ray analysis
EPA	U.S. Environmental Protection Agency
F344	Fischer 344
$FEF_{10\%}$	Forced expiratory flow for the last 10% expired
$FEF_{25-75\%}$	Forced expiratory flow between 25 and 75% of vital capacity
FEV	Forced expiratory volume
FEV_1	Forced expiratory volume at 1 s
$FEV_{25-75\%}$	Forced expiratory volume at 25 to 75% of vital capacity
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ILO	International Labour Organization
IPN	Inhalable Particulate (Sampling) Network
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level

MMAD	Mass median aerodynamic diameter
mppcf	Million particles per cubic foot
mRNA	Messenger ribonucleic acid
n	Number
NA	Not available
N/A	Not applicable
NAAQS	National Ambient Air Quality Standards
NAPEE	National Air Pollution Emissions Estimates
NAQETR	National Air Quality Emission Trend Report
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-observed-adverse-effect level
OAQPS	Office of Air Quality Planning and Standards
OSHA	Occupational Safety and Health Administration
p	Probability
pH	Negative log of the hydrogen ion concentration
$PM_{2.5}$	Particulate matter of mass median aerodynamic diameter ≤ 2.5 μm
PM_{10}	Particulate matter of mass median aerodynamic diameter ≤ 10 μm
PM_{15}	Particulate matter of mass median aerodynamic diameter ≤ 15 μm
PMF	Progressive massive fibrosis
PMN	Polymorphonuclear leukocyte (also called neutrophil)
PORD	Pneumoconiosis and other respiratory diseases
PTEAM	Particle total exposure assessment methodology
PVC	Polyvinyl chloride
SAM	Stationary ambient monitor
Silica F	Fumed silicon dioxide
Silica G	Silicon dioxide gel
Silica P	Precipitated silicon dioxide
SIM	Stationary indoor monitor

SiO_2	Silicon dioxide (silica)
SMR	Standardized mortality ratio
σ_g	Geometric standard deviation
TB	Turberculosis
TDM	Total dichotomous mass
Tg	Teragram
TLC	Total lung capacity
TLV	Threshold limit value
TSP	Total suspended particles
TWA	Time-weighted average
UICC	International Union Against Cancer

GLOSSARY OF TERMS

Acute exposure	A one time or short-term exposure with duration of less than or equal to 24 h.
Aerodynamic diameter (or aerodynamic equivalent diameter)	The diameter of a unit density sphere having the same velocity (due to gravity) as the particle of interest of whatever shape and density, thus avoiding complications associated with the effects of particle size, shape, and physical density.
Aggregate	Can mean either a group of materials or any of several hard, inert substances, such as sand, gravel, or crushed stone, used for mixing with cement.
Amorphous	Having an unstructured molecular arrangement. The atoms and molecules are randomly linked, forming no repeating pattern. See also Noncrystalline.
Atom	A minute particle of matter; the smallest particle of an element that can enter into chemical reactions.
Benchmark dose	The lower confidence bound on the benchmark level of response (defined below).
Benchmark level of response	The exposure concentration or dose as determined by a specific mathematical model that is associated with a predefined effect measure (e.g., 10% response of a dichotomous outcome) as the "benchmark".
Chemical compound	A distinct and pure substance formed by the union of two or more elements in definite proportion by weight.
Chemical element	A fundamental substance that consists of only one kind of atom and is the simplest form of matter.
Chert	Cryptocrystalline silica; composed of extremely fine (submicroscopic) silica crystals.
Chronic exposure	Multiple exposures occurring over an extended period of time or over a significant fraction of the animal's or individual's lifetime.
Clearance	The translocation, transformation, and removal of deposited particles from the respiratory tract.

Compound	See Chemical compound.
Cristobalite	The form of crystalline silica that is stable at the highest temperature. It occurs naturally in volcanic rock.
Critical effect	The first adverse effect, or its known precursor, that occurs as the dose rate increases. Designation is based on evaluation of overall database.
Crystalline	Having a highly structured molecular arrangement. The atoms and molecules form a three-dimensional repeating pattern, or lattice.
Cumulative silica	Expressed in milligrams of silica per cubic meter times years; can be calculated in exposure many ways, but, in general, is an estimate of the average respirable (crystalline) silica concentration a person is exposed to on the job over the course of a working year times the number of years worked.
Cumulative silicosis risk	The probability of developing silicosis given a cumulative silica exposure.
Derived	A substance formed from the products that result when a more complex substance is destroyed. Pure silicon is said to be “derived” from quartz sand.
Diatomaceous earth (or diatomite)	A rock, high in amorphous silica content, formed from the structures of tiny fresh- and saltwater organisms called diatoms. Diatomite has several commercial uses.
Element	See Chemical element.
Epidemiology	The study of the distribution of a disease or a physiological condition in human populations and of the factors that influence this distribution.
Forced expiratory volume at one second	The volume of air that can be forcibly exhaled during the first second of expiration following a maximal inspiration.
Forced vital capacity	The maximal volume of air that can be exhaled as forcibly and rapidly as possible after a maximal inspiration.
Free silica	Information name for a pure crystalline silica, which is chemically uncombined.

Functional residual capacity	The lung volume at the end of tidal expiration (total lung capacity less inspiratory capacity).
Fused silica	The material formed by heating cristobalite to the melting point (1,710 °C) and cooling it rapidly.
Generation	Refers to the branching pattern of the airways. Each division into a major daughter (larger in diameter) and minor daughter airway is termed a generation (numbering begins with the trachea).
Lowest-observed-adverse-effect level	The lowest exposure level at which there are statistically and biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.
Macrophage	A large phagocyte, a type of scavenger cell in the body that engulfs foreign materials and consumes debris and foreign bodies.
Mass median aerodynamic diameter	Mass median of the distribution of mass with respect to aerodynamic diameter. Graphs for these distributions are constructed by plotting frequency against aerodynamic diameters.
Metal	A type of element, such as lead, aluminum, and iron. Metals are usually hard and lustrous, malleable (they can be pounded into sheets), ductile (they can be drawn into wires), and can conduct electricity and heat.
Mineral	Naturally occurring crystalline solids, most of which are made from oxygen, silicon, sulfur, and any of six common metals or metal compounds.
Molecule	The smallest particle of a substance that retains the qualities of the substance and is composed of more than one atom.
Noncrystalline	See Amorphous.
Nonmetal	Elements, such as carbon, silicon, and phosphorus, that do not exhibit the properties of metals, and usually are poor conductors of electricity and heat.

No-observed-adverse-effect level	An exposure level at which there are no statistically and biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. Some effects may be produced at this level, but they are not considered as adverse nor as immediate precursors to specific adverse effects. In an experiment with several no-observed-adverse-effect levels (NOAELs), the assessment focus is primarily on the highest one for a given critical effect, leading to the common usage of the term NOAEL as the highest exposure without adverse effect.
Opal	An amorphous form of silica.
Organic compound	A chemical compound containing carbon.
Phagocytized	To be removed from the body by the action of phagocytes. It is believed that, after exposure to airborne crystalline silica particles, as much as 80% of the particles are phagocytized by alveolar macrophages and eliminated within several months to a year via slow migration from the pulmonary regions of the lungs.
Pneumoconiosis	A condition characterized by permanent deposition of substantial amounts of particulate matter in the lungs and by the tissue reaction to its presence; may range from relatively harmless forms of sclerosis to the destructive fibrosis of silicosis.
Polymerization	A chemical reaction in which small organic molecules combine to form larger molecules that contain repeating structural units of the original molecules. The product of polymerization is called a “polymer”.
Polymorph	Literally "many forms". To be polymorphic means to have or assume several forms. In reference to crystals, it is the characteristic of crystallizing in more than one form. For example, crystalline silica can be in the form of quartz, cristobalite, tridymite, etc.
Portal-of-entry effect	A local effect produced at the tissue or organ of first contact between the biological system and the toxicant.
Precipitated silica	Amorphous silica that is precipitated from either a vapor or solution.

Quartz	The most common type of crystalline silica. Some publications will use quartz and crystalline silica interchangeably, but the term "crystalline silica" actually encompasses several forms: quartz, cristobalite, tridymite, and several rarer forms.
Regional deposited dose	The deposited dose (milligrams per square centimeter of respiratory tract region surface area per minute) of particles calculated for the respiratory tract region of interest, as related to the observed toxicity (e.g., calculated for the tracheobronchial region for an adverse effect in the conducting airways).
Regional deposited dose ratio	The ratio of the deposited dose in a respiratory tract region for the laboratory animal species of interest to that of humans. This ratio is used to adjust the observed particulate exposure effect level for interspecies dosimetric differences.
Reserve volume	Volume of air remaining in the lungs after a maximal expiration.
Residual volume	The lung volume after maximal expiration (total lung capacity less vital capacity).
Respirable crystalline silica (respirable dust)	May be defined as dust that contains particles small enough to enter the gas-exchange (pulmonary) region of the human lung. For the purposes of this document, the term respirable will be used to refer to particles estimated to be less than 5 μm mass median aerodynamic diameter.
Respiratory bronchiole	Noncartilagenous airway with lumen open along one side to alveoli. When walls are completely alveolarized, it is usually referred to as an "alveolar duct"; essentially absent in rats.
Silica	A compound formed from silicon and oxygen. Silica is a polymorph; that is, it exists in more than one state. The states of silica are crystalline and noncrystalline (also called amorphous). However, the term silica is often used to refer specifically to crystalline silica forms. For the purposes of this document, silica implies crystalline silica, unless otherwise specified as referring to amorphous silica. Crystalline silica can take several forms: quartz (most common), cristobalite, tridymite, and four rare forms.

Silica gel	Amorphous silica, prepared in formation with water. Removal of the liquid creates xerogels and further treatment with alcohol creates aerogels. Silica gels are used as drying agents and to alter viscosity of liquids.
Silica flour	Finely ground quartz; typically 98% of the particles are less than 5 μm in diameter.
Silicates	Compounds formed from silicon, oxygen, and other elements. See Silicate minerals and Silicon-oxygen tetrahedron.
Silicate minerals	Minerals containing silicon, oxygen, and a metal or metal compound. Silica tetrahedra form the framework of silicate minerals. Examples are olivine, pyroxene, amphibole, feldspar, and mica.
Siliceous	A term used to describe a rock with a high silica content, especially one containing free silica rather than silicates.
Silicon	The second most common element in the earth's crust (oxygen is the most common). Silicon is a metalloid, possessing some of the properties of a metal and some of the properties of a nonmetal. Pure silicon does not exist in nature. Silicon derived in the laboratory exists as black to gray, lustrous, needlelike crystals, and is an Occupational Safety and Health Administration-regulated substance.
Silicon dioxide	Silica.
Silicones	Synthetic compounds formed from two or more silicon atoms linked with carbon compounds. Most silicones contain oxygen as well. Silicones are formed by a process called polymerization; the molecular structure is a chain, not the tetrahedral shape of the molecules of silica or the silicates. See also Polymerization.

Silicon-oxygen tetrahedron	Silicon and oxygen bond in a paired formation with four oxygen atoms and one silicon atom. Tetrahedron literally means "four surfaces" and refers to the way the molecule looks internally. Picture four spheres (the oxygen atoms) touching a smaller sphere (the silicon atom) held in the pocket in the middle of the spheres. Lines drawn between the centers of the spheres would form a regular, four-sided prism, a tetrahedron. Although many structures are possible in nature, geologists seldom encounter more than a relatively small number, primarily because most rocks are made up of silicate minerals, which combine in the silicon-oxygen tetrahedron. The silicon-oxygen tetrahedron bonds most frequently with sodium, potassium, calcium, magnesium, iron, and aluminum.
Silicosis	One of the more destructive forms of pneumoconiosis (characterized by scarring of lung tissue), which is contracted by prolonged exposure to high levels of respirable silica dust or acute levels of respirable silica dust.
Stable	Possessing an energy state that is balanced and will not change spontaneously (resistant to energy change).
States of matter	A substance can be in a solid, liquid, or gas state. These three are called "states of matter".
Subchronic exposure	Multiple or continuous exposures occurring for approximately 10% of an experimental species lifetime, usually over 3 mo.
Terminal bronchiole	Noncartilagenous airway that conducts airstream to respiratory bronchiole.
Tetrahedron	A solid geometric shape with four surfaces. See Silicon-oxygen tetrahedron.
Threshold	The dose or exposure below which a significant effect is not expected. Carcinogenicity is thought to be a nonthreshold endpoint, thus, no exposure can be presumed to be without some (perhaps theoretical) risk of this adverse effect. Noncancer toxic health effects are presumed to have threshold endpoints; thus, some exposures are presumed to be without risk of adverse effects.
Total lung capacity	The lung volume at maximal inspiration.

Tridymite	A form of crystalline silica. It is found in nature in volcanic rocks and stony meteorites. It also is found in fired silica bricks.
Vital capacity	The maximum volume that can be exhaled in a single breath (total lung capacity less residual capacity).

1. INTRODUCTION

The term "silica" refers to silicon dioxide (SiO_2; Chemical Abstracts Service [CAS] No. 7631-86-9), which occurs naturally in a variety of crystalline and amorphous forms; however, it often is used to refer specifically to crystalline silica forms. Hence, for the purposes of this document, silica implies crystalline silica unless specified as amorphous silica. The principal naturally occurring crystalline silica exists as quartz; three other forms of crystalline silica are cristobalite, tridymite, and tripoli. Although identical chemically (i.e., all are composed of the elements silicon and oxygen in the form of SiO_2), they differ from each other in their crystal parameters. Quartz, cristobalite, and tridymite are interrelated and may change their form under different conditions of temperature and pressure (International Agency for Research on Cancer, 1987). The basic structural units of the silica minerals are silicon tetrahedra shown in Figure 1-1, arranged such that each oxygen atom is common to two tetrahedra. However, there are considerable differences in the arrangements of the silicon tetrahedra among the various crystalline forms of silica (Coyle, 1982). Pure crystalline silica that is not combined with any other elements is sometimes called free silica. When elements such as sodium, potassium, calcium, magnesium, iron, and aluminum are substituted into the crystalline silica matrix, the compound is called a silicate. Examples of silicates are kaolin, talc, vermiculite, micas, bentonite, feldspar, and Fuller's earth (Silicosis and Silicate Disease Committee, 1988). Silicates have their own unique chemical and physical properties distinct from crystalline silica and are not the focus of this document.

Amorphous silica also is composed of SiO_2, but the SiO_2 molecule is randomly linked, forming no repeating pattern. Naturally occurring sediments or rock that contain amorphous forms of silica (i.e., those with nontetrahedral orientations) include diatomite or diatomaceous earth, a hydrated form (e.g., opal), and an unhydrated form, flint (Stokinger, 1981). Diatomaceous earth is a loosely coherent, chalk-like sediment from unicellular algae that contains up to 94% SiO_2 (International Agency for Research on Cancer, 1987). Commonly encountered synthetic amorphous silicas, according to their method of preparation, are SiO_2 gel (silica G), precipitated SiO_2 (silica P), and fumed SiO_2 (silica F). The most outstanding characteristics of

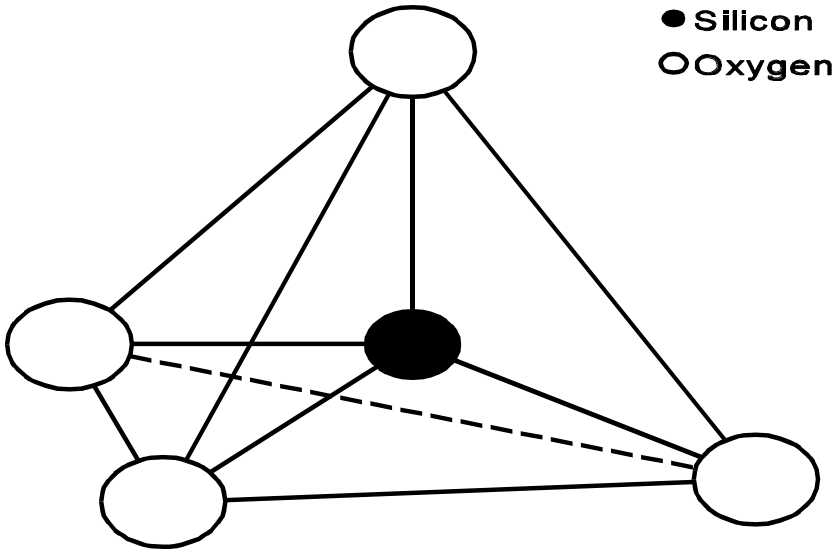

Figure 1-1. Silicon-oxygen tetrahedron.

synthetic amorphous silicas are their small ultimate particle size and high specific surface area, which determine their numerous applications (Stokinger, 1981). The physical and chemical properties of selected crystalline and amorphous forms of silica are presented in Tables 1-1 and 1-2.

Crystalline silica is widely used in industry and has long been recognized as a major occupational hazard, causing disability and deaths among workers in several industries. Chapter 2 reviews important, primarily occupational, national and international regulations and guidelines that pertain to the various forms of amorphous and crystalline silica.

Environmental emissions of silica can arise from natural, industrial, and farming activities. However, no data on ambient air concentrations of amorphous silicas were located, and ambient levels are not well quantified for crystalline silica, principally because existing measurement methods, although capable of distinguishing crystalline silica (e.g., X-ray diffraction), were not designed to deal with the large amounts of nonsilica particles in ambient air. In addition, concern about nonoccupational or ambient silica exposure, specifically crystalline silica, has emerged only recently, principally from populations in the western United States, particularly from California. In an attempt to provide information about ambient crystalline silica and to aid in assessing the

TABLE 1-1. PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED FORMS OF CRYSTALLINE SILICA

Property	Quartz CAS No. 14808-60-7	Cristobalite CAS No. 14464-46-1	Tridymite CAS No. 15468-32-3
Molecular weight	60.09	60.09	60.09
Physical state	Colorless, white, black, purple, or green solid	Colorless, white, or yellowish solid	Colorless or white solid
Crystalline form	Hexagonal; also in anhedral massive form	Octahedral, rarely cubical; also in massive form	Tabular, pseudo-hexagonal; also in massive form
Density	2.65	2.33	2.26
Hardness (Moh's scale)	7.0	6.5	7.0
Solubility			
Water	Practically insoluble; 6 to 11 ppm at 25 °C	Practically insoluble	Practically insoluble
Acids	Soluble in hydrofluoric acid, but insoluble in most other acids	Soluble in hydrofluoric acid, but insoluble in most other acids	Soluble in hydrofluoric acid, but insoluble in most other acids
Organic solvents	Insoluble	Insoluble	Insoluble

Sources: Coyle (1982), American Conference of Governmental Industrial Hygienists (1991), International Agency for Research on Cancer (1987).

risk from environmental exposure, Chapter 3 will review emissions from different sources of silica and estimates of ambient crystalline silica levels using reports in the peer reviewed literature and both national and California data on particulate matter less than 10 μm in aerodynamic diameter (PM_{10}). National emissions and air quality data are published annually by EPA, and California estimates are available from the California Air Resources Board (CARB). In addition, current knowledge of methodologies for estimating crystalline silica levels levels in occupational and ambient environments will be reviewed.

TABLE 1-2. PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED FORMS OF AMORPHOUS SILICA

Property	Precipitated Silica	Pyrogenic Silica[a]	Silica Gels (Dry)
SiO_2 content (%)	80 to 90	99.7 to 99.9	96.5 to 99.6
Physical state	Solid	Solid	Solid
Ultimate particle size (nm)	10 to 25	1 to 100	1 to 100
Aggregate particle size (μm)	1 to 10	2 to 3	3 to 25
Surface area (m^2/g)	45 to 700	15 to 400	200 to 700
Bulk density (g/cm^3)	0.03 to 0.30	0.03 to 0.12	0.1 to 0.8
True density (g/cm^3)	2.0 to 2.1	2.16	2.22
Water solubility (at 25 °C)	80 to 130 ppm[b]	80 to 130 ppm[b]	80 to 130 ppm[b]
pH, aqueous suspension	4 to 9	3.5 to 8.0	2.3 to 7.4
Oil absorption (g/g)	1 to 3	0.5 to 2.8	0.90 to 3.15

[a]Fumed silica
[b]Particle size affects solubility; particles with a diameter <4 nm have a progressively greater solubility than larger particles.

Source: Willey (1982).

Chapter 4 reviews the available laboratory animal and human literature regarding the dosimetry/toxicokinetics of particles, focusing on aspects unique to silica. Most crystalline silica particles released into the environment are >2.5 μm mass median aerodynamic diameter (MMAD) (Davis et al., 1984). As is discussed in Section 4.3.1, particles ≤5 μm MMAD are deposited primarily in the lower respiratory tract when inhaled, and those particles <1 μm MMAD are likely to deposit in alveolar regions. For the purposes of this document, the term "respirable" will be used to refer to particles ≤5 μm MMAD. Because of the large number of sources and widespread emissions, there is potential for some ambient crystalline and amorphous silica particles to be in the respirable range. Further, although most silica particles having an MMAD of >5 μm would be expected to be deposited in the upper respiratory tract (reducing the potential for pulmonary disease), particles ranging from 5 to 10 μm can deposit in the lower respiratory tract under certain conditions (U.S. Environmental Protection Agency, 1982a,b; 1986a).

Chapters 5 and 6 review, respectively, the available human and laboratory animal literature that address the potential for either amorphous or crystalline forms of silica to cause noncancer health effects. Chapter 5 focuses primarily on silicosis and occupational studies but also covers

the potential for silica to cause or exacerbate other diseases and limited data from relevant environmental, clinical, and case reports and studies. This document does not address the potential for any form of silica to cause carcinogenic effects. Although recent experimental evidence suggests that quartz may cause lung cancer in laboratory animals, the mechanisms are not yet agreed on. An increased cancer risk to humans that already have developed adverse noncancer effects from silica exposure (silicosis) has been shown, but the cancer risk to otherwise healthy individuals is not clear. Conversely, the causal relationship between inhalation of dust containing crystalline silica and silicosis, a chronic inflammatory and fibrotic lung disease, is well established. Synthetic amorphous silicas, thus far, have not been shown to present as severe a hazard as quartz and other less ubiquitous forms of crystalline silica.

Although this document is not intended to serve as a complete quantitative health risk assessment, Chapter 7 provides information relevant to the use of occupational studies for estimating the noncancer health risk associated with continuous inhalation of ambient silica. Dose-response data from relatively recent occupational studies in South Dakota, South Africa, and Canada indicate that, for healthy workers in a mining environment, the cumulative risk of developing silicosis is zero for cumulative exposures of less than 1 $mg/m^3 \times$ years. Mining environments generally are considered more hazardous (i.e., more freshly fractured dust, finer particles, more peak exposures) than ambient environmental exposure to silica. The analysis in Chapter 7 indicates, however, that, even if a comparable ambient environment is assumed, the risk of silicosis to an otherwise healthy population continuously exposed for 70 years to the highest silica levels anticipated under the EPA National Ambient Air Quality Standards (NAAQS) for particulate matter (an estimated cumulative silica exposure of approximately 1 $mg/m^3 \times$ years) would be less than 1%. Limitations and discrepancies in the available toxicologic literature for silica and other considerations necessary for extrapolating from occupational to ambient environments are summarized in Chapter 8.

2. REGULATIONS AND GUIDELINES

Because of its potential to cause health effects in exposed populations, a number of regulations and guidelines have been established for silica by various agencies. A summary of values for various silica compounds associated with regulations and guidelines pertaining to silica is presented in Table 2-1. Additional site and operation-specific dust controls are required by some organizations. For instance, the Mine Safety and Health Administration (MSHA) has published guidelines to prevent accidents during operations such as blasting and drilling, which could result in high exposures over short periods of time (Federal Register, 1994). A discussion of such operation-specific regulations is beyond the scope of this document.

TABLE 2-1. REGULATIONS AND GUIDELINES APPLICABLE TO SILICA

Chemical	Agency	Description	Value	Reference
Crystalline Silica				
Quartz	ACGIH	TLV (8-h TWA)	0.1 mg/m^3[a]	American Conference of Governmental Industrial Hygienists (1993)
	NIOSH	Recommended exposure limit for occupational exposure as a TWA for up to 10-h work shift	0.05 mg/m^3[a]	National Institute for Occupational Safety and Health (1990)
	MSHA	Recommended exposure limit in coal mines	0.1 mg/m^3[a]	Villnave et al. (1991)
	IARC	Carcinogenicity classification	Probable human[b]	International Agency for Research on Cancer (1987)
	OSHA	PEL	$\frac{10 \text{ mg/m}^3}{\% \text{ SiO}_2 + 2}$[a,c]	Federal Register (1993)
Crystobalite and tridymite	ACGIH	TLV (8-h TWA)	0.05 mg/m^3[a]	American Conference of Governmental Industrial Hygienists (1993)
	NIOSH	Recommended exposure limit for occupational exposure as a TWA for up to 10-h workshift	0.05 mg/m^3[a]	National Institute for Occupational Safety and Health (1990)
	OSHA	PEL	[d]	Federal Register (1993)
Amorphous Silica				
Fused	ACGIH	TLV (8-h TWA)	0.1 mg/m^3[a]	American Conference of Governmental Industrial Hygienists (1993)
Precipitated and gel	ACGIH	TLV (8-h TWA)	10 mg/m^3[e]	American Conference of Governmental Industrial Hygienists (1993)

TABLE 2-1 (cont'd). REGULATIONS AND GUIDELINES APPLICABLE TO SILICA

Chemical	Agency	Description	Value	Reference
Fumed	ACGIH	TLV (8-h TWA)	2 mg/m^3	American Conference of Governmental Industrial Hygienists (1993)
Amorphous silica			$\frac{80\ mg/m^3}{\%\ SiO_2}$	Federal Register (1993)
Diatomaceous earth (uncalcined)	ACGIH	TLV (8-h TWA)	10 mg/m^3[e]	American Conference of Governmental Industrial Hygienists (1993)
Amorphous silica	IARC	Carcinogenicity classification	Inadequate[f]	International Agency for Research on Cancer (1987)
Particulate Matter (<10 µm)	EPA	National primary and secondary ambient air quality standard	150 $\mu g/m^3$ (24-h average); 50 $\mu g/m^3$ (annual arithmetic mean)	Code of Federal Regulations (1991)

[a]As respirable free silica.
[b]Based on sufficient evidence of carcinogenicity in animals and limited evidence in humans.
[c]Percent quartz is determined from the fraction passing a size selector with specific characteristics defined in Federal Register (1993).
[d]Use one-half the value calculated from the formula for quartz.
[e]As total dust containing <1% crystalline silica.
[f]Based on inadequate evidence of carcinogenicity in animals and humans.

3. SILICA EXPOSURE: CURRENT PERSPECTIVES ON AMBIENT SOURCES, LEVELS, AND MEASUREMENT METHODS

3.1 INTRODUCTION

Recently, public concern regarding nonoccupational or ambient silica exposure, mainly to crystalline silica, has emerged making it important to evaluate background and ambient concentrations. Ambient emissions of silica rarely are estimated or measured in air pollution studies of particulate matter. The potential for and limitations of using data available on airborne silicon concentrations to estimate silica levels will be discussed in Sections 3.4 and 3.5. In general, it is more likely that occupational crystalline silica exposures have been studied. The data available on nonoccupational exposures to other forms of silica are extremely limited. Consequently, this chapter will address crystalline silica only and will describe the state of current information about ambient exposure levels for crystalline silica.

Ambient crystalline silica is emitted into the environment as a fractional component of particulate emissions. California Air Quality Management districts may elect to monitor levels of crystalline silica in addition to other air pollutants. Those activities are the result of Assembly Bill 2588, the "Hot Spots" program (California Code of Regulation, 1989), in which California Air Quality Management districts may specifically monitor crystalline silica levels for emission concentrations and report to CARB. Data are not anticipated in a reportable format in the near future. Although there are limited national data available, the EPA's Inhalable Particulate (Sampling) Network (IPN), established in 1979 to provide a database for review and revision of the U.S. total-suspended-particulate (TSP) standard, provides some information about quartz (Davis et al., 1984).

The critical regulatory particle size is $\leq$10 μm MMAD (as in the PM_{10} NAAQS). The basis for this size cutoff is described in Section 4.2.1. In general, particles of greater size are deposited predominantly in the nasopharyngeal region and cleared rapidly.

Because sources of crystalline silica are not well defined, sources of PM_{10} will be used as surrogates for silica emissions in Section 3.2. Documented PM_{10} and ambient silica levels in the

United States then are reviewed. The relationship between PM_{10} and its crystalline silica component will be examined in Section 3.5 in an attempt to establish mathematical estimates of both airborne PM_{10} and crystalline silica concentrations. Such a connection would allow the prediction of crystalline silica exposures when only PM_{10} exposure information is available. This relationship will vary depending on regional environmental and source characteristics. Limitations of the data are discussed in Section 3.6 and conclusions are presented in Section 3.7.

Pollution sources are viewed as producing either process-stream or fugitive emissions. Process-stream emissions occur when dust releases are inherent to the primary function of an activity (Cowherd et al., 1974). Fugitive emissions are ancillary to the primary activity and are not confined to the process stream. Examples of crystalline silica process-stream emissions would be particles released during brick manufacturing or diatomaceous earth calcining. An example of fugitive crystalline silica emissions would be soil particles containing crystalline silica entrained to the atmosphere by vehicles from unpaved roads. Emission factors relate the pollutant output to the intensity of an activity releasing either process-stream or fugitive emissions (U.S. Environmental Protection Agency, 1985b). In general, mathematical modeling of particulate emissions and regulatory actions have focused on process-stream emissions and have not addressed fugitive dust emissions as discussed below.

The EPA categorizes the sources of air pollutants as transportation, fuel consumption, industrial processes, solid waste (all process-stream emissions), and miscellaneous (fugitive emissions) (U.S. Environmental Protection Agency, 1991a). Estimates of national PM_{10} emissions in these categories have not changed significantly over the past 10 years (U.S. Environmental Protection Agency, 1993). Table 3-1 shows the California 1989 and the national 1989 and 1992 data for PM_{10} emissions from these sources. Components of the miscellaneous and fugitive source categories are forest and structural fires, agricultural and coal refuse burning, and nonindustrial organic solvent use (U.S. Environmental Protection Agency, 1985b). These data are shown in Table 3-2. Sources of ambient dust are fugitive emissions from agricultural tilling, construction, mining, quarrying, paved and unpaved roads, and wind erosion (U.S. Environmental Protection Agency, 1993, 1991a,c). Elucidation of categories primarily responsible for crystalline silica emissions must await development of site-specific linking algorithms between PM_{10} and crystalline silica.

TABLE 3-1. NATIONAL AND CALIFORNIA ESTIMATES OF PM_{10} EMISSIONS FROM ALL SOURCES

	National–1992[a]		National–1989[b]		California–1989[c]	
Source/Category	Tg[d]/Year	Percent[e]	Tg[d]/year	Percent[e]	Tg[d]/year	Percent[e]
Transportation	1.0	2.2	1.5	2.7	0.0920	6.5
Fuel combustion	1.0	2.2	1.1	2.0	0.0400	2.9
Industrial processes	1.8	3.9	2.6	4.8	0.0520	3.7
Waste disposal	0.2	0.4	0.2	0.4	0.0004	<0.1
Miscellaneous[f]	0.7	1.5	0.7	1.3	0.0350	2.5
Fugitive	41.4	89.8	49.3	88.9	1.1510	84.0
Total	46.1		55.4		1.3704	

[a]National Air Quality and Emissions Trend Report, 1992 (U.S. Environmental Protection Agency, 1993).
[b]National Air Pollutant Emissions Estimates, 1940 to 1989 (U.S. Environmental Protection Agency, 1991c).
[c]California Emissions Inventory (California Air Resources Board, 1991).
[d]Tg = teragrams = one trillion (10^{12}) grams.
[e]Percent of total emissions.
[f]U.S. Environmental Protection Agency (1991a) defines "miscellaneous sources" as forest and structural fires, agricultural and coal refuse burning, and nonindustrial organic solvent use. Depending on the reporting agency's classification of data, inclusion within "fugitive" or "miscellaneous" categories may not be uniform.

TABLE 3-2. NATIONAL AND CALIFORNIA ESTIMATES OF FUGITIVE PM_{10} EMISSIONS

	National–1992[a]		National–1989[b]		California–1989[c]	
Fugitive Source Category	Tg[d]/year	Percent[e]	Tg[d]/year	Percent[e]	Tg[d]/year	Percent[e]
Agricultural tilling	6.2	15.0	6.3	12.8	0.157	13.6
Burning:						
Excluding forest fires			0.3		0.036	
Forest fires			0.6		0.037	
Total	NA	NA	0.9	1.8	0.073	6.3
Construction	9.6	23.2	10.2	20.7	0.269	23.4
Mining and quarrying	0.4	1.0	0.3	0.6	NA	NA
Paved roads	7.2	17.4	7.0	14.2	0.603	52.3
Unpaved roads	13.8	33.3	13.9	28.7	0.037	3.2
Wind erosion	4.2	10.1	10.7	21.7	0.013	1.1
Total	41.4		49.3		1.151	

[a]National Air Quality and Emissions Trend Report, 1992 (U.S. Environmental Protection Agency, 1993).
[b]National Air Pollutant Emissions Estimates, 1940 to 1989 (U.S. Environmental Protection Agency, 1991c).
[c]California Emissions Inventory (California Air Resources Board, 1991).
[d]Tg = teragrams = one trillion (10^{12}) grams.
[e]Percent of total emissions.
NA = Data not available.

3.2 SOURCES OF SILICA EMISSIONS

As a first step towards determining potential sources of respirable crystalline silica, sources of PM_{10} were investigated through review of EPA and CARB documents. Emissions data for PM_{10} are provided in the form of weight per unit time. However, various reporting agencies use different units. The EPA uses either millions of metric tons per year or teragrams per year, which are directly interchangeable. The CARB uses English units, tons per day. For the purposes of this report, all values have been standardized for both measures of weight over a 1-year interval and the most scientifically correct measure of metric weight, teragrams (U.S. Environmental Protection Agency, 1991a). One teragram equals 10^{12} g, 1 million metric tons or approximately 1.1×10^6 tons; whereas 1 metric ton equals 1 million g.

Ambient PM_{10} emission estimates from the following activities, occurrences, or processes will be reviewed, as will the origin of the data and a description of the factors governing variability of emissions output. The emission sources to be examined include construction; paved roads; unpaved roads; deicing activities (inclement winter road applications); ceramic, brick, and clay industries; metallurgy; quarrying and mining; agricultural operations; power plant emissions; forest fires; and wind erosion.

Values reported are for 1989. National estimates for 1992 are provided for comparison with 1989 data. Although all agencies collect information from various regions, published reports usually provide no data for specific geographic locations.

Quantitative PM_{10} emissions for the various activities of interest are shown in Tables 3-1 and 3-2. Data are derived from three sources: (1) the California Emissions Inventory (CEI) from CARB (California Air Resources Board, 1991); (2) EPA's 1990 National Air Quality Emission Trend Report (NAQETR) (U.S. Environmental Protection Agency, 1993); and (3) EPA's National Air Pollutant Emission Estimates (NAPEE), 1940 to 1990 (U.S. Environmental Protection Agency, 1991a,c). The EPA and California estimates were not generated using a uniform classification system; thus, discrepancies exist, and the data from the two agencies are not strictly comparable. However, the California data are included to provide an additional perspective.

3.2.1 Construction and Demolition Activities

Table 3-3 shows that PM_{10} emissions from construction and demolition activities are estimated as 10.2 Tg/year nationally and 0.269 Tg/year within California. Variability of crystalline silica emissions from construction activities hinges on soil geology factors because most construction particulates are fugitive releases.

TABLE 3-3. NATIONAL AND CALIFORNIA ESTIMATES OF PM_{10} EMISSIONS FOR SELECTED INDUSTRIES AND FUGITIVE ACTIVITIES[a]

	National		California
Sources	NAQETR[b] (1992)	NAPEE[c] (1990)	CEI[d] (1989)
Construction and demolition	9.6	NA	0.2690
Paved roads	7.2	NA	0.6020
Unpaved roads	13.8	NA	0.0370
Ceramic, etc.	NA	0.368	NA
Metallurgy	NA	0.265	0.0020
Quarrying and mining	0.4	1.410	0.0007
Agriculture	6.2	6.720	0.1710
Power plant	NA	0.419	0.0040
Forest fires	NA	0.600	0.0370
Wind erosion	4.2	10.700	0.0130

[a]Teragrams = one trillion (10^{12}) grams.
[b]National Air Quality Emissions Trends Report, 1992 (U.S. Environmental Protection Agency, 1993).
[c]National Air Pollutant Emissions Estimates, 1940 to 1990 (U.S. Environmental Protection Agency, 1991a).
[d]California Emissions Inventory (California Air Resources Board, 1991).
NA = Data not available.

For major construction activities involved in manipulation of soil surface, emissions factors have been developed that relate the quantity of dust to the extent of construction activity on the basis of the area (acres) involved and the duration of the project. Construction dust emanates from earth-moving operations and construction vehicles traversing unpaved ground. Estimates of PM_{10} emissions are incomplete because they do not address emissions related to usage of specific

construction materials such as sand, gravel, and cement. Estimation of construction emission factors and particulate emissions is tenuous because the rate of emission is affected greatly by control activities such as water application for dust control, time of year, soil geology, and silt content.

Smaller construction activities such as refurbishment of existing structures are not mentioned in the national estimates of fugitive emissions. It is likely that activities such as sandblasting (a common preparatory activity before repainting or resurfacing), modification of walkways or driveways involving the use of concrete, and landscaping (generating soil entrainment) will result in crystalline silica emissions. Construction activities involving "drywall" or gypsum board are likely to have PM_{10} emissions, but so far, there have been no attempts to quantify the silica contributions to these emissions.

Occupational studies of construction dust levels have focused on exposure within closed buildings (Riala, 1988). The exposures have been evaluated either by analysis of settled dust or from samples collected from personal monitors. The estimated fractional crystalline silica content in these environments has been in the range of 2 to 6%. This indoor measure is likely to be an accurate projection of process stream crystalline silica emissions but is unlikely to accurately represent the crystalline silica fraction of outdoor fugitive emissions.

Demolition of senescent buildings has been associated with asbestos exposure. It is likely that demolition activities also may result in exposure to crystalline silica. Release of crystalline silica will be dependent on the crystalline silica fraction within the structure being removed, the use of wetting agents, and the extent of ground disturbance resulting in soil emissions. Demolition of older homes with plaster-containing walls also may result in some PM_{10} and crystalline silica release.

3.2.2 Paved Roads

Table 3-3 indicates that PM_{10} emissions estimates from paved roads are 7.0 Tg/year nationally and 0.602 Tg/year within California. In 1989, California contributed about 8.4% of the nation's total fugitive particulate emissions from paved roadways, a percentage similar to California's proportion of the U.S. population. Crystalline silica emissions derived from paved roads result primarily from reentrainment of soil rather than from other environmental factors.

Vehicular carry-out from unpaved areas is reported to be the largest single contributor to paved roadway particulate emissions (Cowherd et al., 1977). Similar to construction activities, emission factors have been generated that relate fugitive particulate emissions estimates to factors such as vehicle weight and speed, number of wheels, and miles traveled. Components of the roadway particulate emissions include dust generated from tire, brake pad, and roadway wear (Cowherd et al., 1977; U.S. Environmental Protection Agency, 1985a). Although these factors are important in total particles emitted from roadways, tire and brake pad wear may not be as important when considering PM_{10} crystalline silica emissions. Because rubber and tire manufacturing uses amorphous silica, tire particles may contain some silica, though particles are predominantly greater than 10 μm in diameter. In the past, particles emitted from brake pads have been of interest for their asbestos content; a new interest is whether crystalline silica or silicates are being used in newer asbestos-free formulations of brake pad material. Brake manufacturers guard closely the actual formulas used in brake pads, but available industry information reports that crystalline silica, silicates, and ceramics rarely comprise more than 10% and usually less than 5% of the total brake pad material (Patton, 1992).

Other factors influencing paved road emissions are silt content of the surrounding soils (which affects silt loading), frequency of mechanical cleaning of streets, deicing materials and applications, and the asphalt or concrete composition of the street surface (Cowherd et al., 1988). Asphalt streets have been associated with higher silt loading and retention than concrete-surfaced streets. This is likely related to the greater porosity and surface roughness of asphalt roads. As a road ages, surface conditions deteriorate, and, as might be anticipated, particulate emissions increase. Freeways, highways, collector streets, and local streets all show differences in emissions rates. If all other factors are constant, quantities of dust generated from unpaved roadways are greater than quantities from paved roadways (Cowherd et al., 1988).

3.2.3 Unpaved Roads

As shown in Table 3-3, there is an estimated 13.9 Tg/year of PM_{10} emissions from unpaved roads throughout the United States; within California, the estimated release is 0.037 Tg/year.

The surfaces of unpaved roads are the major contributor to particulate emissions (unlike paved roadways in which silt loading is the major contributor). Different types of unpaved roadways (industrial, construction, public, and private) emit particles at different rates, largely

related to the volume of traffic. Control measures such as the application of oil, water, or gravel greatly influence emissions rates. Soil characteristics such as silt, sand and clay content, and annual precipitation levels have more influence on unpaved roadway emissions than on paved roadway emissions (Muleski and Stevens, 1992). Similar to paved roads, vehicular characteristics such as speed, weight, and number of wheels have an influence on unpaved road emissions. Crystalline silica emitted from unpaved roadways will be determined by soil geology characteristics and modifying factors during dust generation (e.g., weather conditions).

3.2.4 Deicing Activities

During winter, deicing is carried out by the application of salt, sand, or other particles to paved roadways. No specific emissions data were available to describe the contribution of deicing materials to PM_{10} emissions. Deicing activities often are included in the emissions estimates for paved roadways (Cowherd et al., 1988). Particulate emissions from deicing applications do not occur at the time of application but rather after the snowmelt has begun to dry. Emission levels rise when road traffic increases the dust concentrations with repeated grinding of deicing sand (in the absence of rain). Deicing agents are estimated to contribute 4 to 5% of the total particulate emissions on paved roads (Cowherd et al., 1988). The PM_{10} component of deicing applications will vary, depending on the tendency of various materials to undergo secondary fractionation into smaller particles from vehicular trauma. In some geographic regions, there may be no crystalline silica component due to the use of volcanic cinder containing little or no crystalline silica. In regions of the United States in which winter ice conditions are common (i.e., north of 35° latitude), particulate emissions from winter deicing activities may be of concern.

3.2.5 Ceramic, Brick, and Clay Industries

As shown in Table 3-3, the U.S. PM_{10} emissions from ceramic, brick, and clay industries are estimated to be 0.368 Tg/year. Typical industrial operations resulting in crystalline silica emissions are kiln drying of clay and brick objects, crystalline sand processing, glass manufacturing, calcining of diatomaceous earth, and pottery manufacturing (Frazier and Sundin, 1986).

Ceramic- and brick-making industries produce process-stream particulate emissions that have a crystalline silica component; variations in their releases depend on the production volume of the specific industry and the degree to which pollution control measures are applied. Specific industry particulate emissions can be estimated using the Compilation of Air Pollutant Emission Factors (U.S. Environmental Protection Agency, 1985a). The fractional component of crystalline silica within PM_{10} also varies with the specific industry. It is anticipated that, within any specific industry, the crystalline silica component will be less variable than the crystalline silica fraction related to soil emissions. However, this assumption is difficult to verify because of the paucity of available data.

3.2.6 Metallurgic Activities

Metal manufacturing industries are estimated to emit 0.265 Tg/year nationally and 0.002 Tg/year in California (Table 3-3). The national emissions can be separated into those originating from smelting and foundry activities (0.136 Tg/year) and the remainder being from unspecified activities. Crystalline silica can be released during different steps in the manufacturing process, depending on its use and on its response to manipulations during manufacturing. Crystalline silica emissions also will depend on the application of particulate pollution control efforts.

Metal industry particulates are process-stream emissions; thus, variations in output change directly with production volume of the industry. Emissions can arise from processing of raw materials (e.g., ore crushing or from the use of siliceous material in the manufacturing process). Production of metallic objects in foundries is often achieved by the process of sand casting. Foundry emissions may be released from interaction of hot metals with sand, production of molds prior to casting, and cleaning of residue from metallic castings. The crystalline silica emissions from ore processing will reflect the technology of manipulation, the crystalline silica content of the parent rock, and available pollution control measures. Occupational exposure to crystalline silica (including tridymite and cristobalite produced at high temperatures) has been documented during the preparation of sand casts, the cleaning of sand residues from fresh castings, sand reclaimation and recycling, and maintenance and repair of crystalline silica brick used in the refractory processes (Mirer et al., 1986). Whether these activities result in environmental releases will be determined by the effectiveness of containment measures.

3.2.7 Quarries and Mining

The national estimated combined process-stream and fugitive emissions of PM_{10} from mining and quarrying are 1.410 Tg/year for the year 1989 as shown in Table 3-3. National and California process stream and fugitive emissions from quarrying and mining activities along with mining subcategories are shown in Table 3-4.

TABLE 3-4. CONTRIBUTING SUBSOURCE ACTIVITIES TO QUARRYING AND MINING PM_{10} EMISSIONS FOR 1989

	National		California
Sources	NAQETR[a] (Tg^d/year)	NAPEE[b] (Tg^d/year)	CEI[c] (Tg^d/year)
Process-stream	NA	1.109	0.0007
Quarrying–sand and gravel	NA	0.620	NA
All mining	NA	0.489	NA
Metal ore mining	NA	0.153	NA
Coal mining	NA	0.336	NA
Fugitive	0.3	0.300	NA
Total		1.409	

[a]National Air Quality Emissions Trends Report 1990 (U.S. Environmental Protection Agency, 1991b).
[b]National Air Pollutant Emissions Estimates, 1940 to 1990 (U.S. Environmental Protection Agency, 1991a).
[c]California Emissions Inventory (California Air Resources Board, 1991).
[d]Tg = teragrams = one trillion (10^{12}) grams.
NA = Data not available.

Because quarrying and mining are inherently dusty and present occupational risks for silicosis (National Institute for Occupational Safety and Health, 1992), it can be anticipated that they will contribute to ambient crystalline silica emissions. Both quarrying and mining generate process-stream and fugitive particulate emissions because both activities involve manipulation of materials inherently high in crystalline silica. There is difficulty separating process-stream emissions from fugitive emissions, and classification may be more arbitrary than factual. Fugitive dust emissions arise from manipulation of outdoor storage piles containing either product or spent tailings. Fugitive emissions tend to be generated after the product has been acquired or produced.

Emissions will vary depending on the nature of material within the storage piles, loading and removal activity, moisture content, precipitation, control procedures, and wind activity (U.S. Environmental Protection Agency, 1977). The crystalline silica component of emissions is determined primarily by the nature of the material involved in the process stream. Ayer (1969) observed that the percent of crystalline silica within larger size particles characteristic of ambient emissions is usually higher in larger size fractions. Ayer suggested that this unequal distribution of crystalline silica within dust may be because quartz, which is harder than most minerals, resists comminution to fine particle sizes. Regardless of source, particles >10 μm contain a greater percentage of crystalline silica than particles <10 μm (Davis et al., 1984; Gillette and Passi, 1988).

3.2.8 Agricultural Operations

Agricultural PM_{10} emissions include fugitive and process-stream emissions; Table 3-3 shows that the estimated national emissions are 6.720 Tg/year. Table 3-5 provides a description of different farming activities that create particulate emissions. It should be noted that, in agriculture, fugitive emissions greatly exceed process-stream emissions, and variability in crystalline silica emissions will be determined primarily by underlying soil geology and regional climatic conditions.

From Table 3-5, it can be noted that the California estimate of PM_{10} emissions from cattle feedlots was greater than that for the entire nation. Although California may have a majority of the nation's feedlots, its emissions cannot exceed the national total. This discrepancy highlights difficulties in comparing values from various agencies when classification systems are not uniform.

Factors governing the variability of dust emissions from agriculture tilling are soil moisture content, inherent soil characteristics such as silt and clay content, tilling implement characteristics such as speed and type, and wind (Cowherd et al., 1974). Interrelated with agricultural particulate emissions are wind-erosion emissions. Depending on the reporting agency's classification of data, assignment to specific categories may not be uniform.

Vegetative materials commonly contain amorphous silica as a result of normal biologic processes that involve the uptake of soluble silicic acid, condensation into oligomeric structures, polymerization, and tissue-specific deposition as amorphous silica (Sullivan, 1980, 1986). If silica-containing living matter is subjected to sufficiently high temperatures, some of the amorphous silica may be transformed into crystalline silica, specifically cristobalite. The

TABLE 3-5. CONTRIBUTING SUBSOURCE ACTIVITIES TO AGRICULTURAL PM_{10} EMISSIONS FOR 1989

	National		California
Sources	NAQETR[a] (Tg/year)	NAPEE[b] (Tg/year)	CEI[c] (Tg/year)
Tillage	6.3	6.300	0.157
Fuel consumption	NA	0.069	0.0002
Burning	NA	NA	0.014
Cattle feedlots	NA	0.019	0.027
Feed and grain milling	NA	0.046	
Grain elevators	NA	0.035	NA
Total		6.469	0.198

[a]National Air Quality Emissions Trends Report 1990 (U.S. Environmental Protection Agency, 1991b).
[b]National Air Pollutant Emissions Estimates, 1940 to 1990 (U.S. Environmental Protection Agency, 1991a).
[c]California Emissions Inventory (California Air Resources Board, 1991).
NA = Data not available.

conversion of amorphous silica to cristobalite during the calcining step during diatomaceous-earth processing was described by Cooper and Cralley (1958). Cristobalite was detected in the ash produced during incineration of rice hulls at high temperatures, although subsequent lowering of the furnace temperature prevented the conversion Rabovsky (1992).

A study of fugitive agricultural dust emissions and resulting crystalline silica emissions was performed by Green et al. (1990). Different farms in Alberta, Canada, were monitored for particulate emissions with background emissions constructed from regional historical data. Dust generation was examined at different times of the year as well as during different tilling procedures (discing, harrowing, planting, plowing, etc.). In addition to area monitors, sampling devices were placed on tractors (near the engine's air intake filter), thus, monitoring dust at the point of highest concentration. In modern agricultural production, closed cab tractors with air conditioning are common. Measurements such as these, taken from outside the cab, may not reflect workplace exposures but may reflect (worst case) environmental levels. Wide variations in levels were detected, with peak TSP levels ranging from 140 to 160 $\mu g/m^3$, depending on the region within Alberta. Background TSP levels ranged from 40 to 80 $\mu g/m^3$; the crystalline silica fraction ranged from 0.85 to 17.5%; and the fraction of particles of respirable size ranged from

50 to 97%. Much of the variability was associated with the individual farm and the crops raised on each.

3.2.9 Power Plant Emissions

Table 3-3 shows that power plant emissions were estimated to contribute 0.419 Tg/year of PM_{10} emissions nationally; within California, there was an estimated release of 0.004 Tg/year. The primary sources of crystalline silica from power plant emissions are spent ash and combustion of materials used in the process of power generation.

Nationally, the majority of power plants rely on the combustion of coal to generate electricity, and the particles emitted reflect the chemical composition of the coal burned (U.S. Environmental Protection Agency, 1991a). Coal combustion usually results in the emission of substantial quantities of particles and other pollutants, but little crystalline silica is emitted. California's contribution to the national PM_{10} from electric utilities is about 1%. Because of California's large population, a parallel demand for electricity is expected, and thus, a greater contribution to the overall national PM_{10} emissions might be expected. However, California's reliance on oil, gas, and hydroelectric generators may explain the lower than anticipated emissions.

Cogeneration of electricity from the burning of agricultural by-products (e.g., incineration of rice-hulls) must address combustion temperature as an important determinant of the crystalline silica type emitted. Although combustion at low temperatures (<700 °C) is not expected to result in a change in the normally occurring amorphous silica, high-temperature incineration ($\geq$800 °C) can cause a conversion of the amorphous silica into cristobalite (Cooper and Cralley, 1958; Rabovsky, 1992).

3.2.10 Forest Fires

As shown in Table 3-3, in 1989, there was an estimated 0.6 Tg/year of PM_{10} emissions from forest fires nationally. In California, PM_{10} emissions from forest fires for 1989 were estimated at 0.037 Tg/year. During combustion, much of the original amorphous silica in the plant will be released in an amorphous form when combustion is at a low temperature; however, the temperatures at the center of the forest may be sufficiently high that some of the naturally

occurring amorphous silica could be converted into crystalline silica (ENSR Consulting and Engineering, 1991; Materna et al., 1992).

Forest fire emissions will vary greatly from year to year due to differences in fire season activity. Substantial regional differences also can be anticipated. It is also likely that variations in combustion temperature and species differences of trees and other vegetation burned will create differences in the crystalline silica content within the PM_{10} emissions.

3.2.11 Wind Erosion

Nationally, there were an estimated 10.7 Tg/year of PM_{10} emissions due to wind erosion in 1989 and 0.013 Tg/year within California (Table 3-3). Wind erosion is the process of particulate aerosol generation from air currents moving over soil. Nationally, fallow agricultural cropland presents the greatest surface area for the action of wind erosion (Cowherd et al., 1988). Particles and crystalline silica also may be released from wind blowing over open storage piles and from industrial discharge. Wind-related industrial emissions most commonly are associated with fugitive releases and, thus, may be overlooked within estimates of industrial particulate emissions.

Wind erosion particulate emissions vary due to soil parameters, climatic factors, geographic features, vegetation type, and farming practices (Cowherd et al., 1974). Because many of these emissions are related to bare ground surface, fallow agricultural land is an important source. Productive agricultural land is also important; emissions factors have been developed that describe the variability of particulate emissions from wind erosion due to crop variety (U.S. Environmental Protection Agency, 1977; Gillette and Passi, 1988). Native vegetation usually provides better protection against wind erosion than do agricultural crops. Additionally, in the agricultural setting, field management techniques (furrow width and depth, field length, presence of wind breaks, implement type, etc.) are important parameters in estimating emissions from wind erosion. Erodibility of the soil is dependent on soil textural class, annual precipitation, and temperature. Geographic features, such as mountains, ridges, plains, and valleys, create patterns in wind flow that result in variable rates of wind erosion (Gillette and Hanson, 1989).

The National Oceanic and Atmospheric Administration considers the Great Plains Region of Texas, Oklahoma, Kansas, and Nebraska (portions of EPA Regions VI and VII) as the major regional contributors to PM_{10} emissions from fugitive dust or wind erosion (Gillette, 1992a). Other data suggest that large populations in California, Nevada, and Arizona (Region IX) also are

impacted by high fugitive dust emissions (see Figure 3-1) (U.S. Environmental Protection Agency, 1991b).

3.3 PM_{10} AMBIENT LEVELS IN NATIONAL AIR POLLUTION DATA

There are two primary (i.e., health-based) NAAQS for PM_{10}: (1) a 24-h average PM_{10} standard of 150 $\mu g/m^3$ and (2) an annual arithmetic mean PM_{10} standard of 50 $\mu g/m^3$. This section provides information on PM_{10} levels within the United States from 1987 through 1993, focusing on those metropolitan areas for which PM_{10} levels exceeded the established annual mean PM_{10} NAAQS of 50 $\mu g/m^3$. Data are from EPA's NAQETRs (U.S. Environmental Protection Agency, 1989, 1990, 1991b,d, 1992, 1993, 1994b).

Figure 3-1 depicts areas that did not attain the PM_{10} NAAQS (either the 24-h or the annual mean PM_{10} standard) in 1990, by emission type. Table 3-6 presents the maximum annual mean PM_{10} levels in metropolitan areas (>500,000 population) that exceeded the 50 $\mu g/m^3$ standard during any year from 1987 to 1993. A metropolitan area has been described generally as a large population center with adjacent communities that have a high degree of economic and social integration with the urban core (U.S. Environmental Protection Agency, 1991c). Of interest is that three of the four metropolitan areas shown in Table 3-6 that registered the highest annual average PM_{10} levels between 1987 and 1993 are in California, and all three of these areas (Bakersfield, Fresno, and Riverside-San Bernardino) were nonattainment areas in 1993 (along with New Haven-Meriden, CT).

The annual arithmetic mean PM_{10} levels measured in Riverside-San Bernardino, CA, are consistently and significantly higher than other metropolitan areas. In the fall of 1990, an EPA particle total exposure assessment methodology (PTEAM) study was conducted in Riverside (population = 139,000) (Pellizzari et al., 1992). Each of 178 nonsmoking residents (aged 10 or older) and their homes (both indoor and outdoor concentrations) were monitored for two consecutive 12-h periods to estimate the frequency distribution of exposure to inhalable particles (<10 μm MMAD). An important finding of this study was that population- weighted mean daytime personal PM_{10} concentrations were 150 $\mu g/m^3$, more than 50% higher than the mean daytime values measured by stationary monitors in the homes or outdoors at the homes and the central monitoring site (Figure 3-2). This suggests that the use of ambient air monitoring to

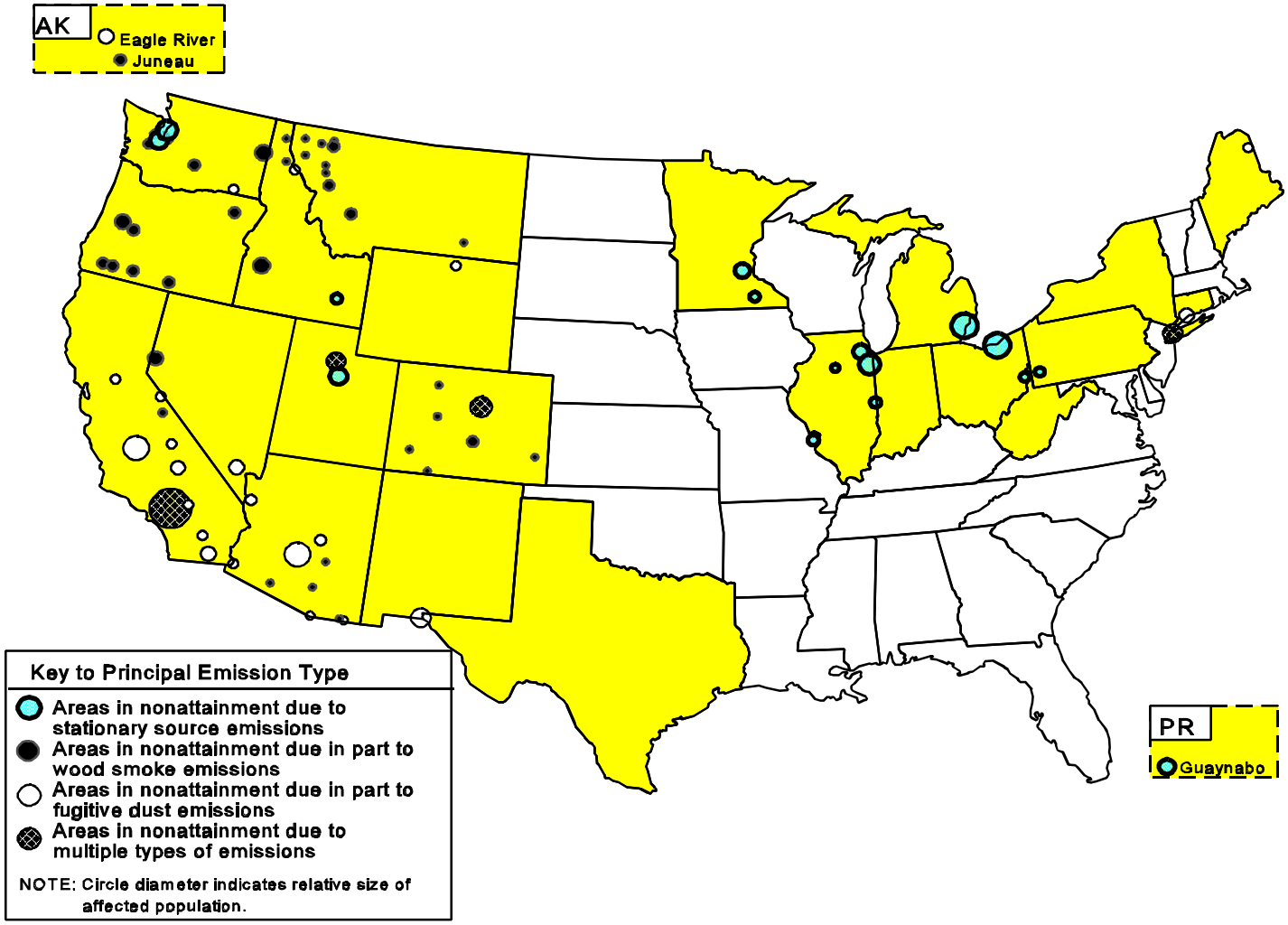

Figure 3-1. Areas designated nonattainment for the PM_{10} National Ambient Air Quality Standards (1990), by emission type (states containing nonattainment areas are shaded).

Source: U.S. Environmental Protection Agency (1991b).

TABLE 3-6. ANNUAL ARITHMETIC MEAN PM_{10} LEVELS IN METROPOLITAN AREAS[a] THAT HAVE EXCEEDED THE 50 $\mu g/m^3$ NATIONAL AMBIENT AIR QUALITY STANDARDS ANY YEAR FROM 1987 AND 1993

Metropolitan Statistical Area	1992 Population	PM_{10} Annual Arithmetic Mean ($\mu g/m^3$)[b] 1987	1988	1989	1990	1991	1992	1993	7-Year Average ($\mu g/m^3$) 1987 to 1993
Atlanta, GA	2,834,000	46	46	34	**51**[b]	36	34	28	39
Bakersfield, CA	543,000	64	61	79	79	70	63	54	67
Birmingham, AL	908,000	52	47	44	45	42	39	36	44
Cleveland, OH	1,831,000	51	57	52	48	56	36	48	50
Detroit, MI	4,382,000	42	52	52	35	42	37	42	43
El Paso, TX	592,000	54	62	69	54	45	44	37	52
Fresno, CA	667,000	63	60	76	66	60	52	53	61
Gary-Hammond, IN	615,000	64	49	47	40	42	39	34	45
Kansas City, MO/KS	1,566,000	75	45	47	43	45	44	44	49
Las Vegas, NV	741,000	43	63	69	69	58	IN	44	58
Los Angeles-Long Beach, CA	8,863,000	68	65	64	55	66	49	47	59
New Haven-Meriden, CT	530,000	58	48	44	41	47	33	53	46
New York, NY	8,547,000	42	56	66	37	IN	28	47	46
Phoenix, AZ	2,122,000	ND	57	70	46	50	34	44	50
Pittsburgh, PA	2,243,000	45	54	43	43	39	34	38	42
Riverside-San Bernardino, CA	2,589,000	90	95	93	80	76	79	73	84
St. Louis, MO/IL	2,444,000	70	69	76	82	49	50	44	63
Salt Lake City-Ogden, UT	1,072,000	53	54	56	33	54	51	42	49
Tucson, AZ	667,000	38	68	52	46	39	32	28	43

[a] Population > 500,000.
[b] Values in bold are for years when the 50 $\mu g/m^3$ NAAQS was exceeded.

ND = Data not available.
IN = Insufficient data to calculate summary statistic.

Source: U.S. Environmental Protection Agency (1989, 1990, 1991b,d, 1992, 1993, 1994b).

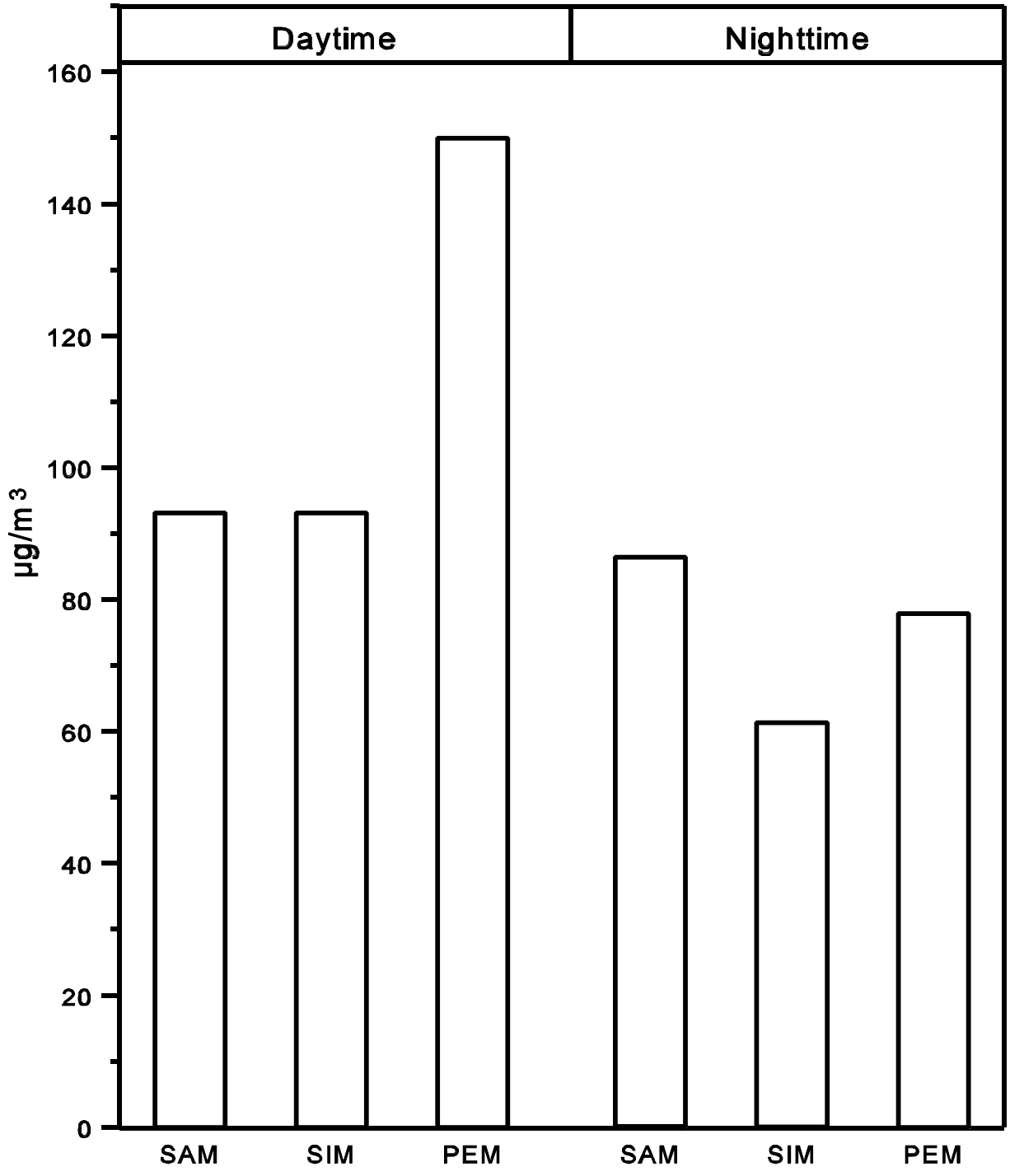

Figure 3-2. Mean outdoor stationary ambient monitor (SAM), stationary indoor monitor (SIM), and personal exposure monitor (PEM) PM_{10} concentrations for 178 residents of Riverside, CA.

Source: Pellizzari et al. (1992).

estimate cumulative exposures does not necessarily result in an overestimate of a population's actual exposure to PM_{10}. Causes of the higher personal exposures found in the Riverside study are not understood completely, but may include various personal activities. For example, persons who engaged in housework (vacuuming, dusting, cooking, etc.) had higher PM_{10} exposures than those employed outside the home.

3.4 MEASURED AMBIENT SILICON AND SILICA DUST CONCENTRATIONS

The Riverside PTEAM study (Pellizzari et al., 1992) also examined various elemental components of PM_{10}, including silicon. The concentration of silicon, the elemental component of crystalline silica, was distributed in a similar manner as PM_{10} (Figure 3-3). Daytime personal silicon concentrations were more than 50% higher than outdoor levels and more than 85% higher than indoor levels. The important point is that indoor levels were not found to be significantly lower than outdoor levels of silica, suggesting that ambient measurements would not necessarily overestimate overall silica exposures.

The EPA's IPN provides one national data set from 1980 for which direct silica particles were obtained (Davis et al., 1984). High-volume and dichotomous particulate samples were collected over 24-hour periods every 6 days at approximately 100 locations throughout the United States. The dichotomous samples from Teflon® filters were analyzed by X-ray fluorescence for elemental confirmation and then for silica quantification by X-ray diffraction. The high-volume filters were analyzed only by X-ray diffraction. Tuscarora sandstone quartz was used as the standard calibration particle with which to compare ambient quartz concentrations. There were 25 IPN cities included in the silica analysis study, although each location did not necessarily have both high-volume and dichotomous samplers. Data were expressed as average quartz levels derived from X-ray diffraction analysis for both fine (PM $\leq$ 2.5µm [$PM_{2.5}$]) and coarse (PM 2.5 to 15 µm [$PM_{2.5\text{-}15}$]) particles by sample type. Tables 3-7 and 3-8 are from Davis et al. (1984) and provide some direct national estimates of airborne quartz in particulate samples.

Table 3-7 shows average concentration of silica (quartz) from dichotomous samples in 22 cities; levels are expressed as coarse quartz (2.5 to 15 µm aerodynamic equivalent diameter [d_{ae}]), fine quartz (<2.5 µm d_{ae}), total dichotomous mass (TDM) (<15 µm d_{ae}), and percentage of

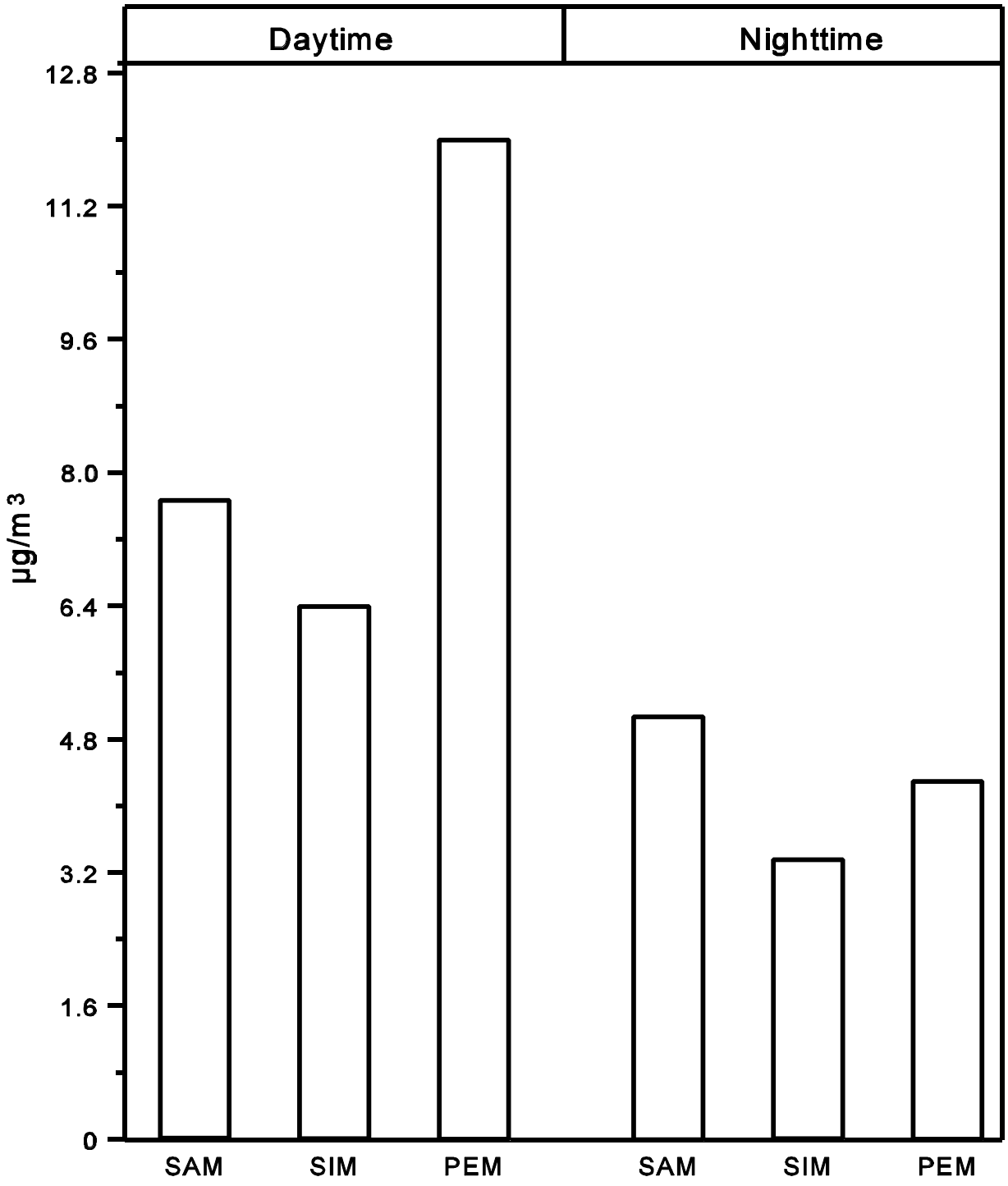

Figure 3-3. Mean outdoor stationary ambient monitor (SAM), stationary indoor monitor (SIM), and personal exposure monitor (PEM) silicon (<10 µm particle size) concentrations for 178 residents of Riverside, CA.

Source: Pellizzari et al. (1992).

TABLE 3-7. AVERAGE QUARTZ CONCENTRATIONS IN AMBIENT AIR FOR SITES IN 22 U.S. CITIES – DICHOTOMOUS SAMPLES

		Coarse Quartz ($\mu g/m^{-3}$)		Fine Quartz ($\mu g/m^{-3}$)		TDM[b] ($\mu g/m^{-3}$)		Quartz Percentage of TDM[b]	
Site	n[a]	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Coarse	Fine
Akron, OH	7	4.2	1.4	<0.1	0.1	71.2	16.1	5.9	<0.1
Boston, MA	1	8.0	-	0	-	140.8	-	5.7	0
Braidwood, IL	1	4.4	-	0	-	57.2	-	7.7	0
Buffalo, NY	14	2.3	1.4	0.1	0.3	83.6	26.6	2.8	0.1
Cincinnati, OH	2	2.6	1.5	0	-	63.2	1.0	4.1	0
Dallas, TX	4	2.6	1.0	0.3	0.3	62.7	22.9	4.2	0.5
El Paso, TX	10	2.2	1.1	0.1	0.1	76.5	43.2	2.9	0.1
Five Points, CA	3	6.6	3.2	1.0	1.2	124.8	84.1	5.3	0.8
Hartford, CT	2	3.0	2.1	0	-	54.8	6.2	5.5	0
Honolulu, HI	1	1.2	-	1.2	-	47.1	-	2.6	2.6
Inglenook, AL[c]	8	5.2	1.7	0.3	0.2	72.6	14.0	7.2	0.4
Kansas City, KS	8	4.7	2.6	0.4	0.4	69.2	28.3	6.8	0.6
Kansas City, MO	3	4.2	3.0	0.1	0.1	58.6	21.6	7.2	0.2
Minneapolis, MN	6	3.7	2.3	0.1	0.1	46.5	7.9	8.0	0.2
Portland, OR	7	1.4	0.6	<0.1	0.1	133.9	122.2	1.0	<0.1
Research Triangle Park, NC	3	0.9	0.5	0.4	0.1	37.0	3.5	2.4	0.1
Riverside, CA	4	3.0	1.1	0	-	106.6	42.2	2.8	0
St. Louis, MO	5	4.4	2.6	0.1	0.1	57.0	11.5	7.7	0.2
San Jose, CA	6	1.9	0.9	<0.1	0.1	67.0	27.3	2.8	<0.2
Seattle, WA	1	1.0	-	0.1	-	36.1	-	2.8	0.3
Tarrant, AL[c]	6	4.3	2.3	1.9	1.0	101.9	57.7	4.2	1.9
Winnemucca, NV	5	5.9	4.3	0.8	0.7	65.7	47.4	9.0	1.2

[a]Number of filters analyzed.
[b]Total dichotomous mass.
[c]North Birmingham.

Source: Davis et al. (1984).

TABLE 3-8. AMBIENT QUARTZ CONCENTRATIONS FROM HIGH-VOLUME FILTER SAMPLES COLLECTED AT 10 U.S. CITIES

Site	Sample I.D.	Collection Date	Filter Load ($\mu g\ cm^{-3}$)	TSP ($\mu g\ cm^{-3}$)	Quartz ($\mu g\ cm^{-3}$)	Quartz (wt %)	Error (wt %)
Akron, OH	GSWS	10/24/80	251.7	58.9	15.8	26.9	6.2
Boston, MA	GNRM	07/02/80	236.3	58.6	9.5	16.2	1.7
	GSXS	09/12/80	205.2	50.3	7.6	15.2	3.8
Cincinnati, OH	GRPV	10/06/80	365.0	86.3	8.3	9.6	2.4
Dallas, TX	GJLE	04/21/80	279.8	69.4	3.6	5.2	0.6
	GJJE	05/03/80	209.2	51.8	3.9	7.6	5.3
El Paso, TX	GHUM	03/04/80	181.3	41.0	4.3	10.6	0.0
	GVOR	12/05/80	263.0	65.2	2.3	3.5	0.4
Hartford, CT	GGUN	02/21/80	380.5	102.9	12.0	11.7	4.1
	GPYY	08/31/80	213.5	50.7	5.1	10.1	5.9
Pasadena, CA	GJOQ	05/03/80	262.5	65.1	2.9	4.4	1.1
	GLZY	06/20/80	434.0	102.0	2.2	2.2	2.4
	GRDG	07/26/80	450.0	102.6	1.6	1.6	0.8[a]
Philadelphia, PA	GFXJ	01/25/80	293.7	71.7	1.2	1.7	0.2
	GGPP	02/06/80	226.7	56.8	4.0	7.0	3.6
	GHZV	03/04/80	358.7	88.7	3.2	3.6	1.4
	GIPM	03/28/80	248.0	66.6	2.1	3.2	0.6
	GJPU	04/18/80	277.0	65.3	2.7	4.2	1.5
	GRMK	08/01/80	483.2	115.8	10.0	8.6	4.0[a]
North Phoenix, AZ	GRWU	09/24/80	323.5	87.2	13.9	15.9	4.2
Portland, OR	GUQK	11/23/80	226.3	56.1	0	0	-

[a]Variance error for single analysis.

Source: Davis et al. (1984).

TDM. In the coarse particles, the mean concentrations ranged from 8.0 $\mu g/m^3$ in Boston, MA, (based on one sample) to 0.9 $\mu g/m^3$ in Research Triangle Park, NC. For the coarse particulate quartz content as a percent of TDM, there was a range of 9.0% from Winnemucca, NV, to 1.0% in Portland, OR. In the fine particulate quartz, the mean levels ranged from 1.9 $\mu g/m^3$ in Tarrant, AL, to zero in several cities. For fine particulate quartz as a percent of TDM, a range was observed from 2.6% in Honolulu, HI, to 0% in Riverside, CA; Hartford, CT; Braidwood, IL;

Boston; and Cincinnati, OH. It is worth noting that of these latter sites, only Riverside had more than two sampling filters analyzed, thus reducing confidence in some low range values. The mean TDM of particles ranged from 140 $\mu g/m^3$ in Boston to 37 $\mu g/m^3$ in the Research Triangle Park. The percentage total quartz in TDM can be obtained by adding the last two columns (i.e., percentage coarse + percentage fine). The average percentage total quartz in TDM for the 22 cities was 5.4%, and the highest percentage total quartz in TDM was 10.2% for Winnemucca.

Table 3-8 includes the findings from cities in which high-volume samples were collected. The highest concentration of quartz was 15.8 $\mu g/m^3$ in Akron, OH, with Portland, OR, showing zero. The highest percentage quartz by weight was 26.9% in Akron, and the lowest was Portland at 0%. Both of these findings are based on only one sample each. The investigators noted that their results were similar to work by Bradway and Record (1976), who, by analysis of elemental silicon with a polarizing optical microscope, reported levels for cities such as Cincinnati (19% quartz), St. Louis, MO (26% silica), and Birmingham, AL (21% quartz). These earlier studies are comparable to levels reported by Davis et al. (1984) for percent quartz in TSP from Akron. Davis and co-workers calculated mean values for all IPN sites and reported that 4.9% of coarse fractions were quartz, whereas 0.4% were quartz in fine particles.

Schipper et al. (1993) compared the quartz concentrations from three Central Valley and two coastal sand and gravel operations in California. In the Central Valley, the silica percentage of PM_{10} air emissions in the quarry pits ranged from 6.0% in Sacramento to 9.1% in Tracy, whereas the silica levels around the crusher ranged from 11.2% in Visalia to 25.5% in Tracy. In the coastal quarries in Monterey and Felton, the portions of quartz were from 14.1 to 16.6% in the PM_{10} samples (Schipper et al., 1993).

A series of particulate air pollution measurements were collected by investigators in several Western locations in which mass balance chemical concentrations were assessed. One of the principal investigators has estimated that measured elemental silicon could be converted to silica by dividing silicon by the total mass of the particle, and multiplying the fraction by 30%–the proportion of crystalline silica (not amorphous silica) in the particle (Watson, 1995). In the discussion that follows of papers published by Watson, Chow, and their colleagues, this conversion factor has been used to estimate the silica fraction. Watson et al. (1988) studied the air pollution levels in several locations in the winter around Denver, CO. The ranges of silica varied from 0.4 to 0.5% in the fine $PM_{2.5}$ emissions (Watson et al., 1988). Chow and colleagues

described the silicon concentrations from PM_{10} samples from several geological sources of particulate air pollution in the San Joaquin Valley, CA, during 1988 and 1989. They reported that silica ranged from 2.0 to 7.8% in both urban and rural locations in the San Joaquin Valley (Chow et al. 1992a). In an extension of the same research project, the investigators confirmed that the silica levels in the PM_{10} fraction ranged from 3% in Fresno and Bakersfield to 4.7% in the rural town of Fellows (Chow et al., 1993). Chow and colleagues (1991) measured silica levels in Phoenix, AZ, in the winter of 1988-1989, and they reported a range from 3.3% in a West Phoenix neighborhood to 6.4% at a gunnery range, a rural site near the city (Chow et al., 1991). Chow et al. (1992b) measured the silica levels in and around Tucson, AZ, in the fall of 1988 and winter of 1988-1989. They reported that silica in the PM_{10} fraction ranged from 4.3% in downtown Tucson to 5.6% in Corona de Tucson neighborhood (Chow et al., 1992b). In the summer of 1987, nine Southern California locations were studied for their silica levels, which ranged from 0.8 to 6.0% in the PM_{10} fraction and from 0.1 to 1.0% in the $PM_{2.5}$ fraction (Chow et al., 1994).

In a 1989 CARB project, Houck et al. (1989) reported on the chemical composition of 40 particulate sources, including dust from agricultural soil, paved and unpaved roads, sand and cinder storage, urban unpaved areas, desert soils, alkaline playa sediment, and emissions from diesel trucks, oil field crude oil combustion boilers, agricultural burning, dairies and feedlots, highway construction, fireplaces, woodstoves, and ski tour diesel buses. It found silicon to be a major elemental component (>1% by weight) in agricultural soil, paved and unpaved roads, sand and cinder storage, desert soil, unpaved urban areas, and construction.

In a report to the Monterey Bay Unified Air Pollution Control District of California, Goldsmith (1991) reported the PM_{10} and crystalline silica levels measured at two sites adjacent to a quarry in central coastal California. The mean PM_{10} concentrations for each site were 18.9 and 18.2 $\mu g/m^3$, with mean crystalline silica concentrations of 1.33 and 1.10 $\mu g/m^3$, respectively. The data show that 6 to 7% of the site-specific PM_{10} was crystalline silica. The emission measurements were taken a short distance from the source at a point of potential human exposure, thus providing a scenario of possible public exposure to crystalline silica. It is expected that the percent crystalline silica within PM_{10} dust will decrease with increasing distance from the source, because larger particles settle with increased distance from the source (Gillette and Passi, 1988; Gillette and Hanson, 1989; Johnson et al., 1992).

A recent study of rice farming commissioned by CARB and conducted by the Division of Occupational and Environmental Medicine at the University of California at Davis (University of California at Davis, 1992) reported ambient dust and crystalline silica levels associated with various rice farming activities. Outside the tractor cab during harvesting, the geometric mean respirable dust level was 1,040 $\mu g/m^3$, and the crystalline silica level was 30 $\mu g/m^3$ (3%). During field preparation for planting, the geometric mean respirable dust was 3,170 $\mu g/m^3$, and the crystalline silica level was 80 $\mu g/m^3$ (2.5%) outside the tractor cab. The geometric means of exposure levels related to crop residue burning were 353 $\mu g/m^3$ for respirable dust and 30 $\mu g/m^3$ (8.5%) for crystalline silica.

3.5 ESTIMATING SILICA CONCENTRATIONS FROM PM_{10} DATA

The current situation that exists for silica is in many ways analogous to the situation that existed for PM_{10} in the early 1980s. Prior to the 1980s, dust concentrations were classified as TSPs, and very little PM_{10} data existed. Subsequent to the revision to the EPA NAAQS for particulate matter, size fractionation became important, and the amount of available PM_{10} data gradually increased to the abundance that exists today. During the interim, before sufficient PM_{10} data had been collected, many different combinations of mathematical formulas, ratios and rate constants were developed to adjust existing TSP and other air quality measurements to predict PM_{10} levels (U.S. Environmental Protection Agency, 1984). Although, as discussed in Section 3.4, some direct measurements of quartz (Davis et al., 1984; Schipper et. al., 1993) and silicon levels (Watson et al., 1988; Chow et al., 1991, 1992a,b, 1993, 1994) in U.S. metropolitan areas exist, the information is somewhat sparse (e.g., limited to a specific region) and dated, and the silicon measurements must be converted to levels of crystalline silica. Thus, approaches to estimating current U.S. silica concentrations from the abundance of PM_{10} data are explored in this section.

An inferential method that has been used to estimate the crystalline silica fraction in ambient PM_{10} is to assay nearby soil or process-stream emissions. An inherent assumption is that the fraction or percentage of crystalline silica within emitted PM_{10} is equivalent to the fraction within the parent source. Although the procedure may be unreliable (Howard et al., 1991), this methodology often is accepted due to lack of alternatives. The ranges of crystalline silica

percentages within ambient emissions estimated by this technique vary greatly. As previously described, Green et al. (1990) demonstrated a difference between parent soil source and ambient crystalline silica source. In addition, it should be recognized that studies of both ambient (Davis et al., 1984) and occupational (Verma et al., 1994) airborne crystalline silica have shown that most airborne crystalline silica is coarse and not respirable (>5μm MMAD). Hnizdo's (1990) epidemiology study of South African gold miners also demonstrated the fallacy of assuming that the fraction of silica in PM_{10} equals that in the parent source. Hnizdo showed that, within gold mines, the parent rock is approximately 60% crystalline silica, whereas the respirable dust within the mines is close to 30% crystalline silica (Beadle and Bradley, 1975).

Other methods have been used to estimate crystalline silica exposure. Samples of settled dust from protected areas can be collected and subsequently assayed for particle size and crystalline silica content (Norboo et al., 1991; Schaefer et al., 1972). Postmortem lung tissue can be analyzed to determine the composition of inhaled particles that have been retained (Norboo et al., 1991; Gylseth et al., 1984; Schwartz et al., 1981; Sherwin et al., 1979; Bar-Ziv and Goldberg, 1974). The latter method will give a measurable evaluation of both respirability and the percentage of particles composed of crystalline silica that are retained. It would not be expected to be a useful indicator of amorphous silica exposure because of the likelihood that these forms would dissolve within months (Reuzel et al., 1991). With additional pathological information, postmortem studies might be used to provide estimates of lifetime crystalline silica dust exposures.

Table 3-9 summarizes the available data for simultaneous crystalline silica and PM_{10} or respirable dust measurements (in micrograms per cubic meter) from various researchers. Review of the relationship between paired measurements will aid in the initial development of a mathematical link between crystalline silica and PM_{10}. The percentage of crystalline silica within air samples can vary from near zero to 60%. The highest value, 60%, was found only in dust storms in foreign countries (Saiyed et al., 1991). Similar levels within U.S. dust storms have been difficult to quantify (Gillette, 1992a). Crystalline silica emissions from agricultural activities ranged from 3 to 17% (Green et al., 1990; University of California at Davis, 1992). Industrial processes, such as quarrying, produce crystalline silica concentrations in the 6 to 12% range

TABLE 3-9. SUMMARY OF PM_{10} MEASUREMENTS AND ASSOCIATED SILICA LEVELS FROM SELECTED STUDIES

References	Mean PM_{10} or Mean Respirable Dust Concentration ($\mu g/m^3$)	Silica Concentrations Reported ($\mu g/m^3$)	Silica as a Percent of PM_{10}
University of California at Davis (1992)			
Harvester	1,040[a]	30	2.9
Crop burn	353[a]	30	8.5
Tractor	3,1 70[a]	80	2.5
Davis et al. (1984)			
Fine (MMAD < 2.5 µm)	24.9	0.29	0.1
Coarse (MMAD 2.5 to 15 µm)	38.6	3.53	7.2
Goldsmith (1991)			
Site No. 1	18.9[b]	1.33	7
Site No. 2	18.2[b]	1.11	6
Green et al. (1990)	140 to 160[c]	1 to 23.8[d]	0.85 to 17.5
Grobbelaar and Bateman (1991)	349 to 844[a] TWA[e]	3.2 to 13 TWA[e]	0.01 to 3.2

[a]Respirable-sized particles ≤5 µm.
[b]PM_{10} or particle ≤10 µm.
[c]Green did not provide a measurement of PM_{10}, but rather a measure of TSP and measurements of percent respirability. From Green's figures, the PM_{10} is being estimated at 85% of the TSP.
[d]The range was calculated using Green's average respirability of 85% multiplied by high and low crystalline silica percentages, multiplied by the high and low TSP measurements reported.
[e]Comparable to NIOSH recommended exposure limit of 50 $\mu g/m^3$ for threshold limit value-time-weighted average.

(Goldsmith, 1991; University of California at Davis, 1992). The research reviewed suggests that a possible upper-bound estimate of crystalline silica near agricultural sites might be approximately 17%.

The consolidation of silica fraction data by industrial activity was considered as a possible refinement of estimates of crystalline silica percentages in PM_{10}. Plausible upper-bound crystalline silica percentages for available activities are 17% for activities involving the burning of agricultural materials; 17.5% for farming activities involving soil manipulation such as plowing and discing; and 7% for quarrying activities (Table 3-9). Other studies, however, indicate that the fraction of silica in PM_{10} samples will be determined more by the composition of the local environment (soil, rock sediment, etc.) than by the activity pursued. Muir (1994) notes the higher fraction of silica in the respirable dust of South African gold mines (reported to be 30% by

Hnizdo et al., 1993) versus Canadian gold mines (reported to be 6.0 to 8.4% by Verma et al., 1989 and Muir, 1994) for similar mining activities. Although the Canadian studies did not report the fraction of silica in the rock being mined, Hnizdo and Sluis-Cremer (1993) reported that the rock mined in South Africa had a very high quartz content, 60 to 90%.

The fraction of dust found to be silica in an occupational setting may not be representative of the ambient environment. Depending on the composition of the dust, the crystalline silica may settle out faster or slower as the dust is dispersed from the site. In this regard, the 7% upper-bound silica fraction estimated by Goldsmith (1991) for two quarry sites in central coastal California may provide a better estimate of ambient exposures because it is based on measurements taken at sites distant from the source and closer to the potentially exposed population.

As indicated by Table 3-1, fugitive sources are the major contributors to ambient PM_{10}. As indicated by Table 3-2, less than 25% of fugitive dust (PM_{10}) comes from construction, mining, or quarrying activities. The remainder comes predominantly from agricultural tilling, road traffic, and wind erosion. Thus, the fraction of dust that is silica can be expected to vary depending on regional soil characteristics and mineralogy. The strong influence of location on quartz fraction within air samples of ambient dust was shown in the Davis et al. (1984) analysis of U.S. metropolitan areas. As shown in Table 3-7 for 22 cities, the average percent quartz in the total dust samples (combining fine and coarse fractions from the dichotomous samplers) varied by more than an order of magnitude, from 1% in Portland (7 measurements) to 10.2% in Winnemucca (5 measurements). This suggests that the use of a single average or upper-bound estimate of the silica fraction within PM_{10} to determine the range of ambient silica levels in the United States from local PM_{10} data would be less accurate than the combined use of local silica fraction data and local PM_{10} data. Annual average PM_{10} data for 1987 through 1993 have been reported for 17 of the cities studied by Davis et al. (1984). Estimations of the silica concentrations in these cities using the silica fraction information reported in Table 3-7 and EPA PM_{10} data (U.S. Environmental Protection Agency, 1989,1990, 1991b,d, 1992, 1993, 1994b) are shown in Table 3-10. This analysis assumes that the quartz fraction in a PM_{10} sample is equal to the quartz fraction in the TDM sample measured by Davis et al. (1984) (reported to be <15 μm MMAD), and that any change in quartz levels over time paralleled PM_{10} changes (i.e., that the quartz fraction has not changed since 1980).

TABLE 3-10. ANNUAL AVERAGE QUARTZ CONCENTRATIONS ESTIMATED FOR U.S. METROPOLITAN AREAS, USING 1987 TO 1993 PM_{10} DATA AND 1980 QUARTZ FRACTION DATA

Site	Quartz[a] Percentage of TDM (Weight %)	7-Year Avg. PM_{10}[b] ($\mu g/m^3$)	Estimated 7-Year Avg. Quartz[c] ($\mu g/m^3$)	1980 Measured Quartz Levels[d] ($\mu g/m^3$)
Akron, OH	6.0	29	1.7	4.2
Boston, MA	5.7	32	1.8	8.0
Buffalo, NY	2.9	28	0.8	2.4
Cincinnati, OH	4.1	33	1.4	2.6
Dallas, TX	4.7	32	1.5	2.9
El Paso, TX	3.0	52	1.6	2.3
Hartford, CT	5.5	28	1.5	3.0
Honolulu, HI	5.2	21	1.1	2.4
Kansas City, KS	7.4	49	3.6	5.1
Kansas City, MO	7.4	49	3.6	4.3
Minneapolis, MN	8.2	33	2.7	3.8
Portland, OR	1.0	34	0.3	1.4
Research Triangle Park, NC	2.5	29	0.7	1.3
Riverside, CA	2.8	84	2.4	3.0
St. Louis, MO	7.9	63	5.0	4.5
San Jose, CA	3.0	31	0.9	2.0
Seattle, WA	3.1	39	1.2	1.1
AVERAGES	4.7	39	1.9	3.2

[a]Davis et al. (1984); quartz as percent of combined coarse and fine dust (<15 µm aerodynamic diameter).
[b]U.S. Environmental Protection Agency (1989, 1990, 1991b,d, 1992, 1993, 1994b).
[c]Estimate of 7-year annual quartz level = 7-year annual PM_{10} level × quartz weight percent.
[d]Davis et al. (1984); combined coarse and fine quartz captured in a dichotomous sampler designed to eliminate particles >15 µm aerodynamic diameter.

Quartz fractions are generally higher in samplers designed to collect larger particle sizes. The percentage quartz in a TSP high-volume filter sampler ranged as high as 26.9% (Table 3-8; Davis et al., 1984). Thus, the assumption that the quartz fraction in PM_{10} is equivalent to the

quartz fraction in a dichotomous sampler designed to collect particles smaller than 15 μm aerodynamic diameter may impart a small amount of error in the direction of high estimates. With this in mind, the 10.2% value for Winnemucca appears to be a reasonable upper-bound estimate of the crystalline silica fraction of PM_{10} in the United States.

Although there are limited and dated direct measurements of crystalline silica levels in the United States, there is enough indirect evidence to indicate that average ambient levels (<15 μm aerodynamic diameter) in U.S. metropolitan areas generally have ranged between 1 and 3 $\mu g/m^3$ and, in most circumstances, are not likely to exceed an 8-$\mu g/m^3$ annual average. Higher levels are possible in certain primarily occupational or agricultural settings. Better quality estimates can be developed as large data sets of paired PM_{10}/silica measurements emerge from California's new silica monitoring. Correlation analysis and linear regression analysis may be appropriate to examine the relationship between crystalline silica and PM_{10} and aid in developing an algorithm to describe the link between crystalline silica and PM_{10}. As an understanding of other variables (e.g., differences in soil and climate) is gained, multiple regression techniques may be used to refine estimates of ambient crystalline silica levels.

An estimate of the ambient background crystalline silica concentration in rural Alberta, Canada, can be calculated using Green et al. (1990) dust parameters. The mean background TSP level from Green et al.'s (1990) Alberta study ranged from 40 to 80 $\mu g/m^3$, with an average near 60 $\mu g/m^3$. Seventy percent of the collected dust was considered respirable (i.e., mass of particles with diameters <5 μm). If half of the remaining 30% of the collected dust is between 5 and 10 μm, then PM_{10} would be 85% of the TSP. The average crystalline silica fraction was about 6% of TSP. Combining all of these parameters results in an estimated Alberta respirable crystalline silica level of 3 $\mu g/m^3$. This estimate appears high relative to the average levels, both measured and estimated, reported for larger ($\leq$10 and $\leq$15 μm aerodynamic diameter) particle size ranges in the United States in Table 3-10, particularly considering evidence that much airborne silica is nonrespirable (Verma et al., 1994; Davis et al., 1984).

Values used for comparison will be dictated by data availability. Some counties or areas may have too few monitors to provide reliable references. Some cities may have monitors only in close proximity to emitters and, thus, provide no information related to background. A question that must be addressed is whether reference levels should represent rural or urban background.

With emissions other than PM_{10}, urban measurements are usually higher than rural measurements, but with PM_{10}, rural regions may have levels higher than urban regions.

3.6 LIMITATIONS OF CURRENT DATA

The lack of current, direct measures of ambient quartz concentrations is a major limitation of the data available for use in estimating U.S. ambient silica concentrations. The more recent data reported by the Desert Research Institute (DRI) (Chow et al., 1991, 1992a,b, 1993, 1994), primarily for the State of California, suffers from the additional limitation of requiring extrapolation from elemental silicon measurements to crystalline silica levels. Watson (1995) has suggested that silicon levels reported by DRI can be converted to crystalline silica by dividing silicon levels by the total mass of the particulate and multiplying the fraction by 30%. The EPA IPN data provided by Davis et al. (1984) suggest, however, that the relationship between silicon and crystalline silica (quartz) content in dust is not constant and may differ significantly depending on the geographic location from which the sample is taken and the particle size range being sampled. Table 3-11 shows the ratios of weight percent quartz to X-ray fluorescence weight percent silicon reported for the 22 metropolitan areas studied by Davis et al. (1984). The ratios for $PM_{2.5}$ samples ranged from 0.3 to 1.1, and the ratios for $PM_{2.5-15}$ samples ranged from 0.1 to 1.2. The ratios were generally lower for the smaller sample size, indicating that other compounds containing silicon may be more prevalent in the smaller size fraction than quartz.

Data from the EPA IPN database (Davis et al., 1984) and DRI (Chow et al., 1994) can be used to investigate the issue of how much the fraction of silica in airborne dust at a particular site can be expected to change over time. That is, information on the relevance of quartz composition data from 1980 dust samples collected by Davis et al. (1984) can be compared to the crystalline silica composition of more current dust samples taken in the same metropolitan areas. No PM_{10} data are available for such a comparison; however, Davis et al. (1984) took four $PM_{2.5}$ 24-h samples in Riverside during the spring and summer of 1980 and analyzed them for quartz and silicon content. Chow et al. (1994) took six $PM_{2.5}$ 24-h samples in Riverside during the fall of 1987 and analyzed them for dozens of chemical species, including silicon. Davis et al. (1984) reported a mean 24-h $PM_{2.5}$ of 35.3 $\mu g/m^3$ and a mean silicon weight percent of 0.8%. Chow et al. (1994) reported a mean 24-h $PM_{2.5}$ of 85.8 $\mu g/m^3$ and a mean silicon weight percent of

TABLE 3-11. COMPARISON OF QUARTZ AND SILICON WEIGHT PERCENTS IN $PM_{2.5}$ AND $PM_{2.5-15}$ SAMPLES FROM 22 U.S. CITIES

Site	n[a]	$PM_{2.5}$ Quartz/Silicon Ratio (wt %/XRF wt %)	n[b]	$PM_{2.5-15}$ Quartz/Silicon Ratio (wt %/XRF wt %)
Akron, OH	1	0.3	7	0.9
Boston, MA	0	NA	1	1.2
Braidwood, IL	0	NA	1	0.8
Buffalo, NY	8	0.7	14	0.8
Cincinnati, OH	0	NA	2	0.4
Dallas, TX	3	0.6	4	0.8
El Paso, TX	8	0.3	10	0.4
Five Points, CA	2	0.4	2	0.4
Hartford, CT	0	NA	2	0.7
Honolulu, HI	1	0.5	1	0.3
Inglenook, AL	7	0.4	8	0.8
Kansas City, KS	8	0.8	8	0.9
Kansas City, MO	1	0.5	3	0.8
Minneapolis, MN	6	0.6	6	0.8
Portland, OR	1	0.6	4	0.1
Research Triangle Park, NC	3	1.1	3	0.7
Riverside, CA	0	NA	4	0.5
St. Louis, MO	4	0.8	5	1.0
San Jose, CA	1	0.3	6	0.4
Seattle, WA	1	0.8	1	0.2
Tarrant, AL	6	0.8	6	0.9
Winnemucca, NE	4	0.4	5	0.6

[a] Number of $PM_{2.5}$ samples for which quartz and silicon levels measured were above the limit of detection.
[b] Number of PM_{10} samples for which quartz and silicon levels measured were above the limit of detection.

NA = Not available.

Source: Davis et al. (1984).

1.6%. This moderate increase in the silicon fraction of $PM_{2.5}$ may have been a reflection of the sample collection site. Although the exact location of the monitor used by EPA in 1980 was not given, the 1987 samples were taken in a location near quarries, cement plants, and agricultural activities, which could have caused the increased silicon content. Chow et al. (1994) also analyzed temporal variations of $PM_{2.5}$ and PM_{10} levels and compositions. They found that $PM_{2.5}$ and PM_{10} levels increased by as much as 100% in some areas between summer and fall, with silicon levels generally rising by a comparable amount. Overall, the limited evidence available appears to indicate that the silicon weight percent within PM samples does not tend to fluctuate markedly with time or temporal variations. The same may or may not be true for the percentage of crystalline silica in PM samples, however, given that ratios of different forms of silica (amorphous and crystalline) and silicates may vary over time, and do vary considerably from one region to another (Davis et al., 1984).

Another limitation of the available data is the fact that neither current nor dated quartz measurements were taken using PM_{10} samplers. The use of samplers designed to collect particles smaller than 15 μm aerodynamic diameter by Davis et al. (1984) may have resulted in a slight overestimate of the crystalline silica levels for particles considered to be inhalable (<10 μm aerodynamic diameter). Although particle size distribution data for crystalline silica in the ambient environment are limited, data from occupational environments suggest that most airborne crystalline silica (quartz) is likely to be in the range of 2.5 to 10 μm aerodynamic diameter. Verma et al. (1994) examined size distributions of airborne dust and its subfractions (including crystalline silica) for several different mining activities. Their results are summarized in Table 3-12. They found that silica in the particle size range of 8 to 16 μm aerodynamic diameter represented just 5% of the total silica sample, whereas silica smaller than 8 μm aerodynamic diameter constituted 50 to 90% of the total silica sample. The 8- to 16-μm size fraction represented less than 10% of all particles in the 0 to 16 μm size fraction. Thus, the amount collected by PM_{10} and PM_{15} ambient samplers may not differ substantially. Silica smaller than 2 μm aerodynamic diameter represented 6 to 16% of the total sample, and the size range from 2 to 8 μm encompassed 43 to 78% of the total occupational sample. As discussed in Section 3.5, limited ambient data suggest that the environmental size distribution for crystalline silica is similar, with even less silica in the $PM_{2.5}$ fraction (Houck et al., 1989; Davis et al., 1984; Chow et al., 1994).

TABLE 3-12. FRACTION OF SILICA IN VARIOUS PARTICLE GROUPINGS FOR MUCKING AND DRY-DRILLING OPERATIONS AT CANADIAN GOLD, URANIUM, NICKEL, AND IRON MINES

	Silica Dust Fraction (%)[a]				
Particle Size (μm d_{ae})	A	B	C	D	E
0 to 0.5	1.2	-	-	-	-
0.5 to 1	3.7	0.9	0.8	2.0	2.1
1 to 2	7.4	6.6	10.8	3.6	14.3
2 to 4	67.9	18.4	32.9	33.4	32.9
4 to 8	9.9	24.2	25.6	13.2	18.1
8 to 16	-	5.5	4.7	6.9	5.2
16 to 32	-	0.1	2.1	1.4	6.4
>32	9.9	44.3	23.1	39.5	21.0

[a]A – Mucking - gold mine.
B – Dry drilling - gold mine.
C – Dry drilling - uranium mine.
D – Dry drilling - nickel mine.
E – Dry drilling - iron ore open pit mine.

3.7 CONCLUSION

As can be seen from Figure 3-1, several areas in California, Arizona, and New Mexico did not attain the PM_{10} NAAQS due, in part, to fugitive dust emissions. Data from Goldsmith (1991) indicate that a reasonable estimate of the crystalline silica fraction in off-site fugitive dust from quarrying activities might be 7%, and data from Davis et al. (1984) indicate that average and upper-bound estimates of the crystalline silica fraction within total dichotomous mass (<15 μm d_{ae}) samples from 22 metropolitan areas are 5 and 10%, respectively. Because these estimates were calculated directly from ambient measurements, and because TDM samplers are likely to collect a higher silica fraction than PM_{10} samplers, 10% is considered a reasonable upper-bound estimate of the silica fraction within PM_{10} samplers.

Data from direct sampling (Davis et al., 1984) indicate that ambient quartz levels in U.S. metropolitan areas average around 3 $\mu g/m^3$ and generally do not exceed 8 $\mu g/m^3$. Table 3-10 illustrates that estimates of current levels using 1980 silica fraction data from Davis et al. (1984) and current PM_{10} data are slightly lower. However, because of the uncertainties associated with

this analysis (discussed in Section 3.6), the direct measures of ambient quartz levels, despite being somewhat dated, are preferred as realistic and conservative estimates of ambient crystalline silica levels.

It is possible that continuous individual exposures are lower for individuals that spend very little time outdoors. However, this is not at all obvious given the findings of the EPA PTEAM study (Pellizzari et al., 1992), which suggest that indoor and outdoor exposures to particles composed of silicon are not markedly different. Daytime exposures to PM_{10} and silicon measured via personal monitors were more than 50% higher than values measured by stationary monitors located both indoors and outdoors.

As the database for ambient PM_{10} and crystalline silica levels is expanded or detailed, site-specific data are available, the predictor values can be adjusted to improve accuracy. Individual situations should be evaluated because process-stream activities and natural conditions may lead to locally higher concentrations.

4. DOSIMETRY AND TOXICOKINETICS OF CRYSTALLINE AND AMORPHOUS SILICA

4.1 INTRODUCTION

The physical properties, sources, and environmental fate of various forms of crystalline and amorphous silica are described in Chapter 2. This chapter begins with a review of studies that have examined the toxicokinetics following exposure to the various forms of silica and ends with a discussion of the contrasts between the dosimetry and toxicokinetics of silica and other particles. Other EPA documents, however, have addressed extensively the toxicokinetics of particulate matter (U.S. Environmental Protection Agency, 1982a, 1986b, 1994a, 1996). Thus, this chapter will focus primarily on aspects of particle pharmacokinetics that are unique to silica.

4.2 LUNG DEPOSITION AND CLEARANCE

The respiratory tract in both humans and experimental animals can be divided into three regions on the basis of structure, size, and function: (1) the extrathoracic region, which extends from just posterior of the external nares to just anterior of the trachea; (2) the tracheobronchial region, defined as the trachea to the terminal bronchioles (where proximal mucociliary transport begins); and (3) the pulmonary region, including the terminal bronchioles and alveolar sacs. The thoracic region is defined as the tracheobronchial and pulmonary regions combined. The anatomic structures included in each of these respiratory tract regions are illustrated in Figure 4-1. The retained dose of an inhaled agent in each of these regions is governed by the exposure concentration, by the individual species anatomy (e.g., airway size and branching pattern) and physiology (e.g., breathing rate and clearance mechanisms), and by the physicochemical properties (e.g., nonnormalized aerodynamic size distribution, solubility, surface chemistry, reactivity) of the chemical (U.S. Environmental Protection Agency, 1982b, 1994a).

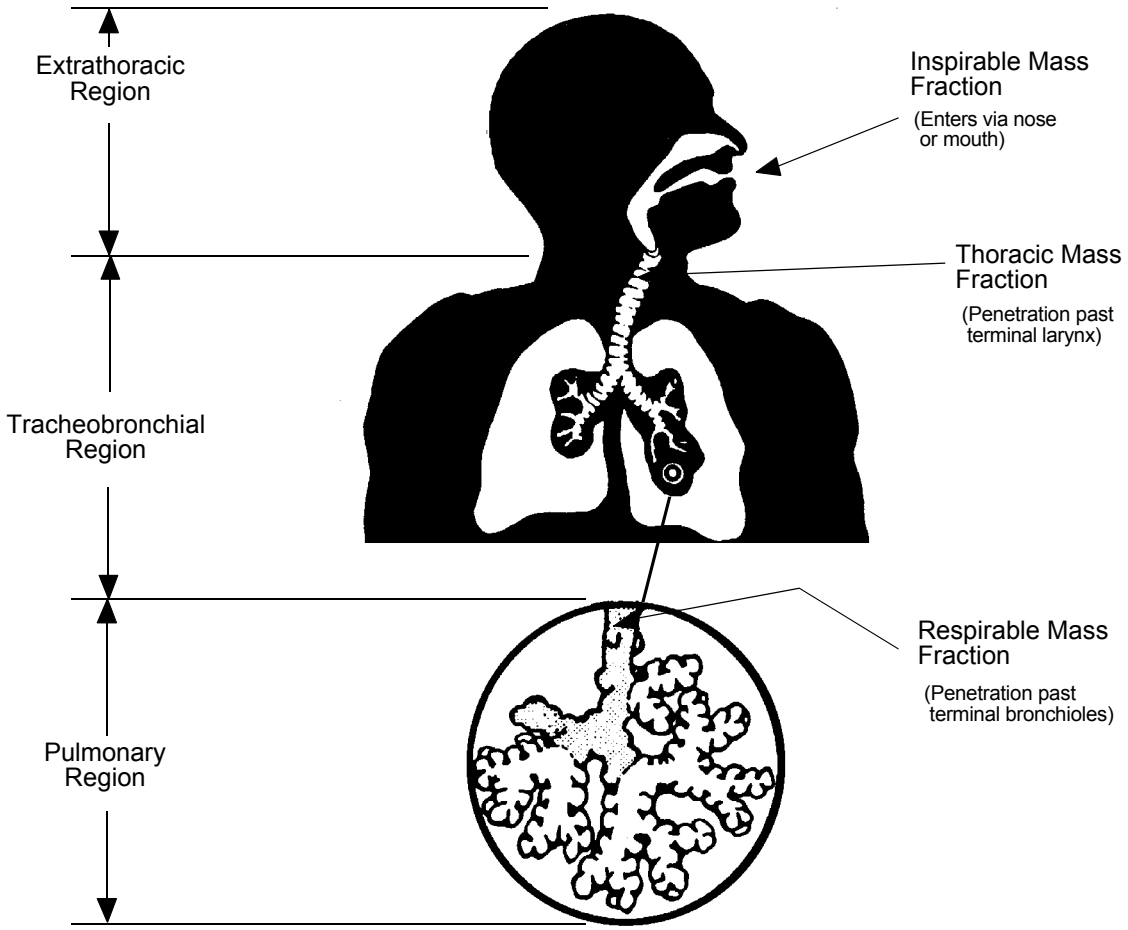

Figure 4-1. Diagrammatic representation of three respiratory tract regions.

In a series of studies of human lungs from lifetime nonsmokers, a distinct correlation of airway generation and particle concentrations was noted with different types of particles. Silica was concentrated in the airways, whereas silicates (kaolinite and mica) appeared in increasing concentrations as the airway diameter narrowed; these silicates constituted an even portion of total particles in the parenchyma (Churg and Stevens, 1988). It is not within the scope of this document to address completely all factors impacting lung deposition and clearance of insoluble particles. This section will review briefly the silica-specific human and laboratory animal literature that exists. Current efforts to model the distribution and clearance of inhaled crystalline silica are described, and the properties of crystalline silica that may account for its slow clearance relative to other insoluble particles are discussed.

4.2.1 Humans

Figure 4-2 presents pulmonary and tracheobronchial deposition in humans of monodisperse particles of 0.1 to 20 μm diameters as a fraction of the number of particles entering the mouth or nose. After inhalation, respirable size particles (≤5 μm MMAD) of silica predominantly deposit and accumulate in the pulmonary region (i.e., gas-exchange region or alveolar region) of the lung and distribute throughout the lung and associated lymph tissue. More recent data suggest that deposition of submicron particles, primarily from diffusion, can be as high as 50% (normalized to the amount entering the lungs) in the pulmonary region of the lungs (under sedentary conditions) (Martonen and Katz, 1993). In humans, inhaled airborne dust particles between about 5 and 10 μm MMAD are predominantly deposited in the tracheobronchial region (i.e., between the pulmonary region and the larynx) and cleared by ciliary movement of the epithelial cells lining the airways. Alveolar particle deposition is enhanced when breathing via mouth rather than nose (Figure 4-2). Particles deposited in the alveoli can be engulfed by macrophages and then transported to the bronchioli or to the interstitial tissues and the lymphatic vessels (U.S. Environmental Protection Agency, 1994a).

Elimination of particles from the pulmonary region of lungs of humans and laboratory animals generally occurs in two phases. The rapid phase usually is completed within 72 h, with clearance of the recently deposited particles in the ciliated airways, either by transportation in the mucociliary stream or by solution and absorption (minor factors for silica particles due to their low solubility). In contrast, the slow-phase removal of deposited particles from the pulmonary region occurs over several months or even years. Slow-phase pulmonary clearance of insoluble particles is primarily via lymphatic drainage and phagocyte activity followed by the slow migration of alveolar macrophages (Guidotti et al., 1986; Wright, 1978).

The cytotoxicity of silica to the macrophages (see Section 5.2) affects silica's retention and clearance (Jones et al., 1988; Pratt, 1983; Muhle et al., 1989). A review by Ziskind et al. (1976) showed that patients with silicosis usually had a least twice as much crystalline silica in their lungs as normal individuals. The upper limit of crystalline silica in the normal human lung is 0.2 g, whereas, in silicotic lung disease, it may increase to 15 to 20 g (Ziskind et al.,

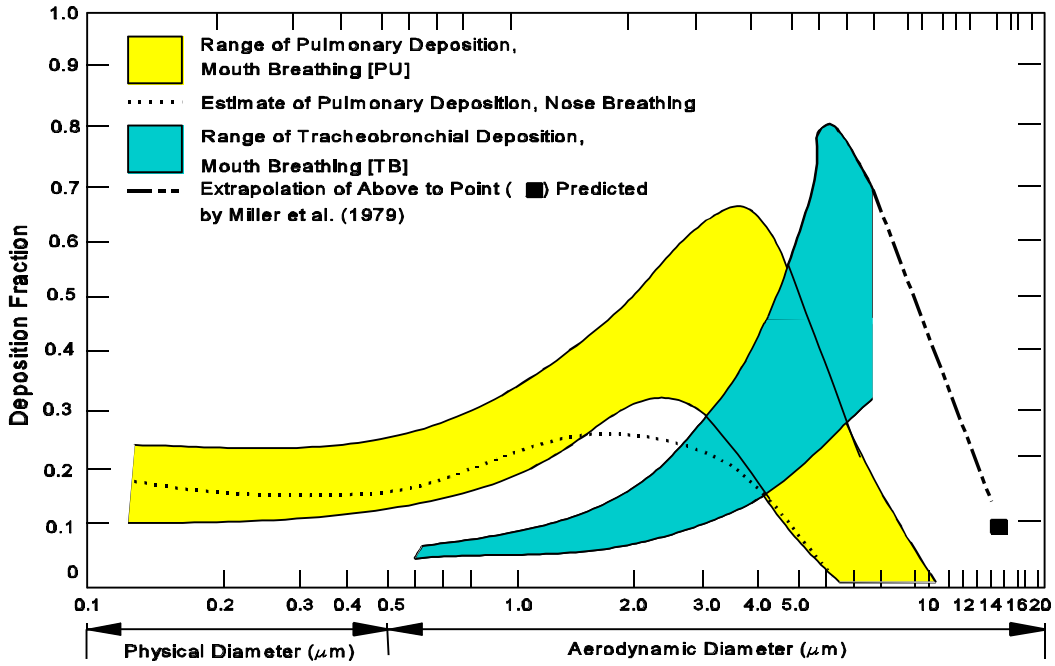

Figure 4-2. Regional deposition in humans of monodisperse particles by indicated particle diameter for mouth breathing (pulmonary and tracheobronchial) and nose breathing (pulmonary). Deposition is expressed as the fraction of particles entering the mouth or nose. The pulmonary region (PU) band indicates the range of results found by different investigators using different subjects and flow parameters for PU deposition following mouth breathing. The tracheobronchial region (TB) band indicates intersubject variability in deposition over the size range measured by Chan and Lippmann (1980).

Source: U.S. Environmental Protection Agency (1994a).

1976). Also noted in silicotic patients were increased kidney weights; for example, the silicon content of renal biopsy material in a patient with acute silicoproteinosis was 200 ppm (dry weight), in contrast to reported normal values of approximately 14 or 24 ppm in patients with chronic renal failure (Saldanha et al., 1975).

4.2.2 Laboratory Animals

Most of the data regarding silica deposition and clearance have been generated in laboratory animal studies. Laboratory animal studies, however, must be interpreted cautiously with regard to environmental exposures because of the possibility of "particle overload".

A complete discussion of this effect is beyond the scope of this document, but reviews are available (Morrow, 1992, 1994; Mauderly et al., 1990). The basic issue is whether the toxicity observed is compound-specific or generic overloading of clearance mechanisms because of high concentrations of respirable dust, which can result in excess retention and can reduce the accuracy of linear exposure-response extrapolations to low levels. Morrow (1992) estimates that overloading can occur when the average volumetric load exceeds 60 μm^3/macrophage. Clearance ceases entirely when the volumetric load exceeds 600 μm^3/macrophage (Morrow, 1988). The concentration at which overload occurs, however, is species dependent, with rats being much more sensitive than hamsters (Saffiotti et al., 1993). In fact, it has been suggested that lung overload in rats is not directly relevant to larger mammals and humans (Snipes, 1995). To a certain extent, this particle overload phenomenon may account for interstudy variations observed in experimental studies of different species.

Raabe et al. (1988) measured particle deposition of aluminosilicate aerosols in the pulmonary, bronchial, tracheal, laryngeal, and nasal-pharyngeal regions of the respiratory tract of several laboratory animal species. The percentage deposited in the pulmonary region of mice, rats, rabbits, hamsters, and guinea pigs was highest (ranging from about 7 to 45%) for particles ≤ 1 μm aerodynamic resistance diameter (d_{ar}). Mean deposition percentages for 1- to 5-μm d_{ar} particles were lower (ranging from about 0.2 to 7.0%), and a very small fraction of particles >5 μm d_{ar} was deposited in the pulmonary region (<1%) of these species. Relative to human pulmonary deposition (see Figure 4-2), rodents retain higher fractions of $\leq$1-μm d_{ar} particles and smaller fractions of >5-μm d_{ar} particles, with greater fractional deposition of 1-to 5-μm d_{ar} particles. Heppleston (1963) exposed rats by inhalation to 4.0 mg/m^3 silica (particle size 0.5 to 5 μm) in the form of Belgian glass sand for periods ranging from 0.5 to 40 h. The initial deposition of silica was highest in the tracheobronchial ciliated air passages; it also was seen throughout the acini, where the extent of deposition decreased as the respiratory airways proceeded distally. The distribution of particles was not uniform between the different acini, and, 2 to 3 mo following cessation of exposure, aggregates were formed, primarily in the proximal alveolar ducts but also in the distal portion of the acini.

Inhalation studies with rats reviewed by International Agency for Research on Cancer (1987) indicate that the long-term clearance of quartz after inhalation is slow and biphasic, whereas amorphous silica dusts are cleared more rapidly. The absolute amount of silica dust

eliminated increased with lung burden, but the efficiency of the elimination was either constant or decreased with time. Rats, exposed to an aerosol of respirable (MMAD not given) α-quartz particles for 6 h/day on 8 consecutive days and studied up to 1 year after exposure, cleared most silica from the lungs and showed signs of dust overload (Davis, 1986). There was an exponential clearance of silica over the first 3 or 4 mo, but approximately 20% of the initial silica load was still present 6 and 12 mo after exposure. The half-life lung clearance of rats exposed via inhalation to an amorphous silica suspension (Ludox™) at concentrations up to 150 mg/m^3 was about 50 days (Kelly and Lee, 1990).

A study by Pratt (1983), showed that the total silica content in the lungs of guinea pigs exposed by inhalation for up to 2 years to a cristobalite sample or to amorphous silica (at dust concentrations of 150 mg/m^3 or 100 mg/m^3, respectively) increased linearly over 21 mo, without evidence that lung retention rates changed with time. These exposure concentrations are well above levels that caused dust overload effects in rats (Davis, 1986; Privalova et al., 1987). The maximum lung content of cristobalite was only 68 mg/lung, whereas that of amorphous silica was 120 mg/lung. The total amount of accumulated silica varied inversely with the degree of pulmonary damage. The authors suggested that silica dust producing cell damage may be more efficiently cleared from the lung than are the less toxic amorphous forms. However, this difference also could be due to different rates of deposition for the two dust forms. The cristobalite sample, which was 45% cristobalite and 55% diatomaceous earth, was significantly coarser (and less likely to deposit in the lungs) than the amorphous silica, which contained 100% diatomaceous earth. Also, tissue changes induced by cristobalite could have altered particle deposition.

In a long-term inhalation study with guinea pigs, Schepers (1981) compared the amount of silica retained as a result of 8-h/day exposures to amorphous silica (Hi-Sil™ 233) with that retained during inhalation of quartz dust for a comparable 12-mo period. Guinea pigs that inhaled quartz dust at a concentration of 106 mg/m^3 retained between 500 and 600 mg of silica, whereas less than 10 mg of dust was retained in those that inhaled 126 mg/m^3 of amorphous silica. After 12 mo of exposure, the relative silica content (silica mass/lung mass) decreased in guinea pigs exposed to quartz dust, but continued to increase slowly in the animals exposed to the amorphous silica. This difference was explained by an increasing nonsiliceous materials content (e.g., collagen, minerals) in the lungs of the quartz-exposed animals associated with the progressive

deposition of fibrous tissue in the lungs. Six months after cessation of exposure, the silica content of the lungs of Hi-Sil™ 233-exposed animals was similar to that of untreated controls. This lack of accumulation may be due, in large part, to the higher solubility of amorphous silica compared to quartz (Reuzel et al., 1991). By comparison, the elimination of silica from the quartz-exposed guinea pigs was negligible, and the silicotic lesions continued to progress during this elimination phase.

As is discussed in Chapter 5, Section 5.2.3, alveolar macrophages play an important role in the cellular responses to silica and in the development of fibrotic lesions associated with silicosis. A frequently cited study by Brody et al. (1982) provides one example of this research. In rats exposed by inhalation to 109 mg α-quartz/m^3 for 3 h, particles were distributed on alveolar duct surfaces, primarily on those closest to terminal bronchioles. The percentage of silica-containing macrophages on alveolar surfaces increased from 36% immediately after exposure to 66% during the 24 h following exposure; this high level was maintained for 24 days and then decreased to 25% 42 days after exposure. The percentages of silica-containing macrophages recovered by lavage were similar to those observed in situ. Three days after exposure, some silica particles had been translocated to the alveolar interstitium. Vincent and co-workers suggested that the sequestration of insoluble particles in this fashion plays an important role in the kinetics of accumulation and clearance of dust from the lung (Vincent et al., 1987; Vincent and Donaldson, 1990).

Differences in deposition and clearance between quartz and three amorphous silicas, Aerosil™ 200, Aerosil™ R 974, and Sipernat™ 22S, were noted in a subchronic inhalation study with rats (Reuzel et al., 1991) (see Chapter 6, Section 6.4, for additional experimental details). Aerosil™ 200 is hydrophilic and is the most widely used form of amorphous silica. Aerosil™ R 974 is produced by a chemical treatment of Aerosil™ 200 that transforms the material into a hydrophobic state. Sipernat™ 22S has the same specific surface area as Aerosil™ 200.

High concentrations of silicon were detected in the lungs and lung-associated lymph nodes of rats exposed to quartz, both at the end of the 13-week exposure period and at all stages of the 1-year postexposure period. Much lower concentrations were detected in the lungs of animals treated with amorphous silicas. Of the groups exposed to amorphous silicas, the highest particulate concentrations were seen in the lungs and lymph nodes of rats exposed to Aerosil™ R 974 at the end of exposure, with smaller amounts still present at Weeks 13 and 26

postexposure. In most animals, all three amorphous silicas were cleared completely from the lungs by Week 39 of the postexposure period.

Accumulations of macrophages laden with fine granular material and the presence of all silicas tested in the regional lymph nodes indicated an active role of the macrophages in lung clearance in the Reuzel et al. (1991) study. Quartz and Aerosil™ 200 induced the most pronounced alveolar macrophage induction including increased neutrophil count, increased lung collagen content, accumulation of intra-alveolar granular material, persistent focal interstitial fibrosis, and cholesterol clefts. These findings were detected at the end of exposure and during the postexposure period, despite the fact that Aerosil™ 200 was cleared the fastest of all silicas tested. The other amorphous silicas induced only slight response to alveolar macrophages. Differences in physical or chemical properties of the surface of the particles may have accounted for the differences in macrophage response and clearance rate of the amorphous silicas. The small particle size of the amorphous silicas had relative surface areas about 10- to 1,000-fold greater than that of quartz. On the basis of this difference in relative surface area, the amorphous silicas can be expected to exhibit greater solubility than the quartz particles. In addition, mucociliary clearance of the quartz versus amorphous test materials may have been different (Reuzel et al., 1991).

To summarize, laboratory animal particle inhalation studies must be interpreted cautiously, taking into account the particle's surface chemistry and size, physiological characteristics of the test species, and the potential for particle overload. Rodents tend to retain a larger fraction of $\leq$1-µm d_{ar} size particles and a smaller fraction of >5-µm d_{ar} size particles. In general, amorphous forms of silica are cleared more rapidly than are crystalline forms. This may be due to the higher solubility of amorphous silica (Reuzel et al., 1991). In addition, alveolar macrophages play a major role in the clearance of either form of silica, and the cytotoxicity of crystalline silica may hinder clearance mechanisms, particularly in the second phase of long-term silica clearance.

4.3 TOXICOKINETICS

4.3.1 Absorption and Distribution

After a postexposure period of about 2 to 3 mo, most of the deposited silica aggregate in the proximal alveolar ducts and in the distal portion of the acini (Heppleston, 1963). Crystalline

forms of silica are not particularly soluble in the lung and are not absorbed and distributed as readily. However, secondary evidence in humans indicates that some silica is transported to the kidneys of silicotic patients. Kidney weights of silicotics are higher than normal (Saldanha et al., 1975), and the silicon content of renal biopsy material in a patient with acute silicoproteinosis was 200 ppm (dry weight), in contrast to reported normal values of approximately 14 or 24 ppm in patients with chronic rental failure. Much of inhaled silica is eventually transported via alveolar macrophages to the lymph nodes. Reuzel et al. (1991) noted that silica content of the lungs declines rapidly after exposure but declines very slowly from lung-associated lymph nodes. No information was located on the distribution of silica to other organ systems.

4.3.2 Excretion

Data regarding the excretion of silica in laboratory animals and humans are limited. According to King et al. (1933a,b), quartz is "slightly" soluble in body fluids and is readily excreted in the urine as silicic acid after absorption following inhalation or ingestion. More recent rodent ingestion studies (Federation of American Societies for Experimental Biology, 1979) found that 95% of silica is not absorbed and is excreted in the feces unmetabolized; 4% is excreted in urine, and 1% remains in tissues.

5. HUMAN STUDIES OF NONCANCER EFFECTS OF EXPOSURE TO SILICA

5.1 INTRODUCTION

The health effects of occupational silica exposure probably have been known since humans began to mine and smelt precious ores, to make glass, and to cut stone, all of which produced high dust levels and, consequently, dust diseases in the lungs (Raffle et al., 1987). The industrial revolution brought power tools to the workplace, resulting in high dust exposures in occupations such as knife grinding, mining and tunneling, metallurgy, flint grinding, pottery making, and sandblasting. Workers in many of these dusty industries had severe respiratory diseases that shortened their lives markedly compared to employees in other trades (Raffle et al., 1987). Discovering and understanding the role that silica played in conditions variously named "miners' phthisis", "potters' rot" or "potters' asthma", or "industrial consumption" did not occur until the first decades of the 20th century. In 1915, the British physician Edgar Collis demonstrated that the lung disease of many "dusty trades" workers was silicosis (or silicotuberculosis), and that it was caused by the inhalation of "free" or crystalline silica dust (Collis, 1919). A great deal has been learned about industrial exposure to silica dust during the 20th century. However, deficiencies remaining in national surveillance systems (Valiante and Rosenman, 1989) and the insensitivities of current diagnostic techniques (Hnizdo et al., 1993) still hamper efforts to determine the prevalence of silicosis in the United States. Recent occupational studies by Hnizdo and Sluis-Cremer (1993), Muir et al. (1989a,b), Ng and Chan (1994), Rice et al. (1986), and Steenland and Brown (1995a,b) provide important evidence of the exposure levels that can cause silicotic effects. By way of contrast, there is much less information about ambient exposures and their possible chronic health effects.

5.2 MECHANISMS AND MANIFESTATIONS OF OCCUPATIONAL SILICA HEALTH EFFECTS

Occupational exposure to respirable particles of crystalline silica or its polymorphs, cristobalite and tridymite, produces several well known conditions: silicosis, silicotuberculosis, enlargement of the heart (cor pulmonale), interference with the body's immune system (scleroderma), and damage to the kidneys. Information on silica health effects was obtained from the work of several experts (Ziskind et al., 1976; Seaton, 1984; Peters, 1986; Silicosis and Silicate Disease Committee, 1988; Balaan and Banks, 1992), from which much of the material in this section is drawn. Silica-related health effects are likely to be detected among active or retired workers in the following industries: abrasives and blasting; boiler and tank scaling; brick, tile, and clay production; cement production; ceramics; coal mining; diatomaceous earth calcining; enameling; farming; foundry work; glass making; metal ore mining and milling; paint blending; pharmaceuticals; quarrying and tunneling; sandblasting; scouring powder manufacturing and use; silica flour fillers; and synthetic mineral fibers production (Peters, 1986). There may be as many as 2 to 4.3 million U.S. workers either currently or previously exposed to silica on the job (National Institute for Occupational Safety and Health, 1991).

Because of difficulties with recreating historical measurements and dust monitoring techniques, research is just beginning to quantitate the precise level of crystalline silica leading to specific degrees of disease. Most investigators believe that the degree of morbidity increases with both increased intensity of dust exposure and cumulative duration of exposure (Davis, 1986; National Institute of Occupational Safety and Health, 1974; Heppleston, 1984; Rice et al., 1986). Other factors such as particle size, worker susceptibility, the age of crystalline surface since fracture (Vallyathan et al., 1988, 1993; Vallyathan, 1994; Shoemaker et al., 1995) , percentage of silica within total dust, and contributions of different polymorphs (Guthrie and Heaney, 1995, in press) influence the degree of risk for many of the diseases discussed below.

5.2.1 Acute Silicosis

Acute silicosis (or silico-proteinosis as it is referred to in some texts) is a rare and highly fatal disease and is the result of intense and massive overexposure to respirable-sized, high quartz content dust over a short time. Acute silicosis is the reaction of the lung to acute dust injury, resulting in the filling of air spaces with fluid containing lipid-rich protein debris from fractured

cells in the respiratory tract. Clinically, the condition is similar to pulmonary edema and includes shortness of breath, with fluid accumulations in the upper and middle areas of the lungs. The worst cluster of acute silicosis in the United States occurred during the building of the Gauley Bridge hydroelectric tunnel at Hawk's Nest, WV, during the Depression years of 1930 and 1931. In this disaster, there were 2,000 African-American and white tunnel construction workers digging through high-silica rock without any respiratory protection. As a result, an estimated 400 men died on site, and 1,500 were disabled with acute silicosis (Cherniak, 1986). Despite the rarity of such clusters, another was described from 1990 to 1993 with over 100 acute and accelerated cases of silicosis among Mexican sandblasters in Midland-Odessa, Texas (Fleming et al., 1990; Wiesenfeld et al., 1993; National Institute for Occupational Safety and Health, 1992).

5.2.2 Accelerated Silicosis

Accelerated silicosis is less devastating, but often is diagnosed in studies of acute silicosis. Accelerated silicosis is the result of exposure to high concentrations of silica over a period of 5 to 10 years. It is a disease that is more prevalent in occupations without proper respiratory protection, including sandblasting and silica flour production (Seaton, 1984). Silico-proteinosis and accelerated silicosis both are attributed to freshly fractured crystalline silica, which has greater toxicity than aged silica (Vallyathan et al., 1993). If the initial exposure is high enough, progression of the disease and premature death from respiratory failure can occur in as little as 10 years, even if a worker is removed from sources of silica dust exposure.

5.2.3 Chronic Silicosis

Chronic silicosis is the most common fibrotic lung diseases arising after 10 or more years employment at low dust concentrations and is characteristic of U.S. workplace exposures during and after World War II. This critical effect is the primary focus of the remainder of this document because it is the first chronic adverse health effect observable from inhalation of crystalline silica as exposure concentration or dose rate increases. Workers in the "dusty trades" may complain of symptoms such as dry cough, production of sputum (sometimes bloody), and shortness of breath during exertion and have reduced pulmonary function and possibly right heart enlargement. These conditions result from a restrictive lung disease characterized by the presence of patches of

fibrotic scarring ($\approx$1 to 3 mm in diameter) in the lung tissue at the ends of the alveolar sacs. Silicosis arises from exposure to particle sizes ($\leq$10 μm) of quartz coming into contact with pulmonary tissue. This particle and lung tissue interaction stimulates the recruitment of pulmonary macrophage cells and consequent production of interleukin 1, platelet-derived growth factor, β-transforming growth factor, and fibronectin. The importance of pulmonary macrophages in the development of silicosis is well established (Heppleston et al., 1963, 1984). In the process of phagocytosis of inorganic particles, macrophages become activated and release an array of mediators capable of injuring the lung parenchyma and promoting the growth of mesenchymal cells. Macrophages recovered from nonsmoking individuals exposed to silica release two- to threefold more oxygen radicals than normal macrophages, including superoxide anion and hydrogen peroxide (Rom et al., 1987). Immunohistologic evaluation of lung specimens of individuals with silicosis demonstrated intense staining for fibronectin (a glycoprotein that plays a role in the development of fibrosis) in regions of fibrosis (Wagner et al., 1982).

Silica particles are cytotoxic to macrophages, and this interaction results in added release of fibrogenic factors such as interleukins, growth factors, and fibronectin. These factors stimulate increased collagen production by fibroblasts. The injured macrophage also may be involved in the development of silicoproteinosis, seen in acute silicosis. As reported by Schwartz (1994), the injured macrophage may not be able to degrade secreted surfactant material, which leads to alveolar accumulation of surfactant lipoprotein in the lungs. The hyalinization of collagen produces a network of silicotic lesions. As the silicotic lesions grow, larger patches of pulmonary tissue become fibrotic scars, which over time become chronic silicosis.

Although diagnostic sensitivity is low (Hnizdo et al., 1993), chest X-ray evidence combined with a history of silica exposure remain the predominant means of identifying silicosis. Small discrete opacities (silicotic nodules) approximately 1 to 3 mm in diameter are seen in the upper half of the lung fields, increasing in size and number as the disease progresses (Peters, 1986). The opacities appear in lymphatics around blood vessels, beneath the pleura in the lungs, and sometimes in mediastinal lymph nodes. The nodules may fuse, resulting in progressive massive fibrosis (Menzel and Amdur, 1986). Tuberculosis (TB) infection was a common concern after diagnosis, but the availability of anti-TB drugs, such as isoniazid, has reduced these secondary risks.

Along with lengthy occupational silica exposure and respiratory symptoms, diagnosis of chronic silicosis is confirmed with a positive X ray. The radiology community has agreed on a grading convention developed by the International Labour Organization (ILO) for assessing the severity of silicosis lesions (International Labour Organization, 1980). The X-ray opacities can range from mild (up to 1.5 mm) to moderate (1.5 to 3.0 mm) to severe (3 to 10 mm). These opacities are different from the diffuse lung changes that occur with age and cigarette smoking, but over time differentiation may be difficult. Chronic silicosis in its simplest form can be detected by X ray in the absence of any physical symptoms or clinical abnormalities. There is autopsy evidence of simple silicosis in Vermont granite workers having neither symptoms nor radiographic findings of silicosis (Craighead and Vallyathan, 1980). Extensive research among South African gold miners shows that X rays only predict about 20 to 40% (depending on the reader) of those with true silicosis (slight to marked) when compared to autopsy results. This misclassification (or under-ascertainment) of disease is reduced when the cumulative exposure to silica dust is high, and the resultant disease is marked (Hnizdo et al., 1993). Diagnosing simple silicosis may be made difficult by confounding from smoking. However, Hnizdo et al. (1993) and the U.S. Surgeon General's Office on Smoking and Health agree that cumulative levels of silica exposure are the best predictors of silicosis risk (U.S. Department of Health and Human Services, 1986; Hnizdo et al., 1993).

Simple silicosis may progress to produce progressive massive fibrosis (PMF), even after removal of the individual from workplace exposure to silica dust. Progressive massive fibrosis also is referred to as complicated or conglomerate silicosis. In some workers with chronic fibrotic disease, there is a tendency for the silicotic lesion to coalesce, so that at autopsy a mixture of conglomerate PMF lesions with smaller fibrotic nodules is observed. With chronic silicosis, some small opacities coalesce into larger ones, greater than 10 mm in diameter, resulting in restricted lung volume, decreased pulmonary compliance, and poor gas exchange (Balaan and Banks, 1992).

5.2.4 Sequelae of Silicosis, Including Tuberculosis, Silico-Tuberculosis, Cor Pulmonale, and Other Conditions

This section is included in order to provide a complete discussion of health effects associated with silica exposures. It should be recognized, however, that the effects and interactions discussed have been noted only following high-level occupational exposures to silica

(principally in mining environments). There is little evidence available relevant to the potential for low-level ambient exposures to cause similar effects.

Occupational studies have found that the major source of co-morbidity with silicosis is infection by Mycobacterium tuberculosis (TB). Early descriptions of dust diseases of the lung did not distinguish between TB and silicosis, and, as Seaton (1984) noted, most fatal cases described in the first half of this century were a combination of silicosis and TB. Currently, there is effective therapy for TB, but because of reactivation of old TB infections and sharing of living quarters with an infected individual, TB remains a potentially serious complication to workers with silicosis (Cowie, 1994). When examining mortality risks after filing Workers' Compensation claims in California from 1946 to 1975, Goldsmith et al. (1995) reported that male silicotics die of TB at a rate 50 times greater than that of the general U.S. population. Because silicosis is prevalent in the dusty trades, it means that it is a disease of working people, some of whom are recent immigrants to the United States from countries where the TB is endemic. Seaton mentions other opportunistic infections as a consequence of silicosis: Mycobacterium kansasii, Mycobacterium aviumintracellulare, nocardiosis, sporotrichosis, cryptococcosis, and aspergillus may invade the injured lung of the worker with silicosis (Seaton, 1984).

Air entering the lung's protective skin, producing a collapsed lung (pneumothorax), is a serious complication of PMF. It is rare in simple silicosis, but more common in PMF complicated by emphysema.

The heart muscle works harder when the pulmonary tissues are injured, so another complication of silicosis and other restrictive lung diseases, such as emphysema, is enlargement and weakening of the right chambers of the heart. This condition is called cor pulmonale, which was detected more frequently in older cohorts of silicotics than is seen currently in occupational medicine practice (Balaan and Banks, 1992).

5.2.5 Auto-Immune Diseases and Nephritis

In addition to the well-documented pulmonary toxicity resulting from inhalation of crystalline silica dust, there are indications that repeated exposure to high concentrations of crystalline silica also may be associated with autoimmune manifestations (Sanchez-Roman et al., 1993; Steenland and Goldsmith, 1995) and renal damage (Goldsmith and Goldsmith, 1993; Silicosis and Silicate Disease Committee, 1988) in association with or in the absence of pulmonary

disease. In a review of diseases associated with silica exposure, the Silicosis and Silicate Disease Committee of the National Institute for Occupational Safety and Health (NIOSH) (1988) reported that mild focal, segmental, proliferative glomerulonephritis and tubular lesions have been found in a small number of patients with accelerated silicosis and in others with a history of dust exposure but with no pulmonary disease. Of 20 seriously ill silicotic patients examined by Saita and Zavaglia (1951), 20% exhibited albumiuria, 40% azotemia, and 45% impaired urine concentration. Osorio et al. (1987) presented a case report of a foundry worker with extensive silica exposure, who developed glomerulonephritis and progressive renal failure in the absence of pulmonary effects; a renal biopsy detected silica within the renal tissues. Giles et al. (1978) described massive proteinuria and renal failure in a sandblaster with acute silico-proteinosis. Another case report described nephropathy in a worker who had been exposed to high levels of silica dust while refurbishing furnaces and boilers (Saldanha et al., 1975). The clinical symptoms were albuminuria and hypertension in the absence of pulmonary disease. The authors speculated that the pathological alterations observed in the glomerulus and proximal tubule may be due to the direct toxic action of silica because significant silica concentrations were observed in renal biopsy material. Although none of the studies elucidated the mechanisms through which silica was transported to the kidneys, the chemical may have been swallowed and entered the systemic circulation.

Since 1914, there have been case reports in the literature linking silica exposure and silicosis with auto-immune disorders and systemic sclerosis, a thickening of the skin with joint and muscle pain and weakness. In the last few years there is increasing evidence from research studies supporting the hypothesis that either occupational silica exposure or silicosis was linked to a wide variety of known or suspected auto-immune disorders, including rheumatoid arthritis, systemic sclerosis (scleroderma), systemic lupus, Sjogren's syndrome, and glomerular renal disease (Steenland and Goldsmith, 1995).

In a recent study, Sanchez-Roman et al. (1993) examined an "opportunistic sample" of 50 workers that had been employed at a scouring powder factory in Seville, Spain. The workers were responsible for grinding and handling a powder that was composed of 90% silica. No exposure levels were provided (the plant was closed at the time of the report), and no controls were identified. The authors diagnosed systemic collagen disease (Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, overlap syndrome, and undefined collagen diseases) in 32

of the workers, a proportion far in excess of that observed in the general population (Sanchez-Guerrero et al., 1995). Of the 32 affected workers, 14 (44%) were identified as silicotic from radiological examinations of the lungs (International Union Against Cancer [UICC] classification). Of the 18 workers without auto-immune or collagen diseases, only 4 (22%) were identified as silicotic from X rays.

The mechanisms that link occupational silica exposure with the development of silicosis and auto-immune conditions are not fully understood. However, Haustein and colleagues (Haustein et al., 1990) have proposed possible pathways for silica-induced scleroderma, a process that is associated with the induction of silicosis. Scleroderma is proposed to arise from exposure to respirable particle size (≤ 10 μm) quartz coming into contact with pulmonary tissue. This stimulates the recruitment of macrophages and consequent production of interleukin 1, platelet-derived growth factor, β-transforming growth factor, and fibronectin. Recruitment of macrophages to engulf the silica particle leads to the destruction of macrophage cells, recruitment of more macrophages to attack the particles, stimulation of collagen, and the hyalinization of collagen to form a silicotic networks. The cycle of production and destruction of macrophages releases hydrolases and proteases leading to the generation of free oxygen radicals, and some particles and macrophages are transported to pulmonary lymph nodes. The macrophage recruitment and destruction cycle and the presence of particles in the lymph system stimulate the production of T helper cells and B cells and, ultimately, activation of the immune system (Guidotti et al., 1986). Immune activation is linked to a variety of humoral responses: hypergammaglobulinemia, production of rheumatoid factor, antinuclear antibodies, and release of other immune complexes. These immuno-stimulatory states lead to rheumatoid arthritis and poly-arthritis; connective tissue disorders such as systemic lupus, Sjogren's syndrome, polymyositis, and scleroderma; and glomerulonephritis (Seaton, 1984; Silicosis and Silicate Disease Committee, 1988; Haustein et al., 1990).

Silica's effects on the immune system also may lead to kidney disease and kidney damage. Thus, being a silica-exposed worker may increase the risk of several types of kidney disease, including end-stage renal disease requiring dialysis (Goldsmith and Goldsmith, 1993; Steenland and Brown, 1995a).

5.3 CASE STUDIES OF ENVIRONMENTAL SILICA/PULMONARY CONDITIONS

Epidemiologic and clinical studies of occupationally exposed cohorts comprise most of the human exposure data associated with crystalline silica. Occasionally there have been case reports of pulmonary ailments suggestive of silicosis or fibrotic lesions related to ambient dust exposure; most of these reports have been from underdeveloped arid portions of the world and are lacking control patients or specific silica dust exposure assessments (Bar-Ziv and Goldberg, 1974; Nouh, 1989; Norboo et al., 1991; Saiyed et al., 1991). Many of these reports also do not differentiate clearly between outdoor occupational exposures and ambient background environments.

Bar-Ziv and Goldberg (1974) described the results of 54 autopsies of nomadic Bedouins from the Negev Desert of Israel. The authors detected silica dust particles in the lungs of 46 of the subjects, and, although the investigators did not detect fibrotic silicosis, they described a condition termed as "simple siliceous pneumoconiosis". These findings were confirmed by a parallel radiology study of 18 Bedouin women by Hirsch et al. (1974), who reported fine diffuse reticulation and micronodular opacities. Bar-Ziv and Goldberg noted that these findings may be due to domestic work done by Bedouin women who clean tents, cook, tend sheep, and spin wool. Although desert dust is assumed to play a role in this benign condition, the women's work activities suggest that this observation is not truly an environmental lung disease, but may be occupational.

Evidence for environmental silicosis was presented by Tosi et al. (1986). They compared the lymph nodes of 12 lung cancer cases determined to have had no occupational silica exposure, with six lung cancer patients with both occupational silica exposure history (miners) and silicotic lymph nodes and six lung cancer patients with no silica occupational exposure history and no silicotic lymph nodes. All of the 12 patients being compared to controls had either peribronchial, mediastinal or hilar silicotic lymph nodes. Although the authors suggested that all 12 cases lacked any occupational exposure history, 6 of the patients were classified as either farmers or woodworkers, occupations that can involve high levels of silica dust exposure. The occupations of the other six patients, housewife, barman, car washer, bailer, and merchant, are less likely to have involved silica exposure.

Nouh (1989) described four cases of nonoccupational pneumoconiosis among Saudi Arabian desert dwellers. The author referred to this condition as "desert lung syndrome", and only one individual (a shepherd) reported occupational exposures.

Grobbelaar and Bateman (1991) described a condition called "Transkei silicosis". The authors studied 25 South African women with this syndrome and seven control women from urban areas of Xhosa, South Africa. They concluded that silica dust produced during domestic grinding of corn and biomass cooking fires may cause this respiratory condition, which they suggest be named "hut lung". From local dust samples, the investigators concluded that the quartz levels were not sufficiently high to produce occupational silicosis, although they mentioned that one grinder was exposed to silica levels similar to that of gold miners. Although hut lung may exist, it appears to be related to domestic work, rather than being true environmental silicosis.

Saiyed et al. (1991) conducted a silicosis prevalence study within Himalayan villages where dust storms are rare (Saboo), moderate (Shey), and severe (Chushot). A random sample of residents over the age of 50 years was evaluated in each city. Pulmonary symptoms were significantly greater in Shey and Chushot than in Saboo. The authors reported radiographic prevalence of silicosis of 2.0% in Saboo, 20.1% in Shey, and 45.3% in Chushot. The silica fraction in dust storms ranged from 60 to 70%, and there were additional exposures from soots and dust produced in residential cooking. Assuming all villages were involved with farming to the same degree, these data appear to have an environmental component.

Norboo et al. (1991) compared the prevalence of silicosis among 50- to 62-year-old residents of two Indian Himalayan agricultural villages: one with frequent dust storms (Chushot) and the second, a control (Stok), with fewer storms. Using chest films and International Labour Organization (ILO) (1980) criteria, Norboo and co-workers found a greater proportion of X-ray opacities consistent with silicosis in Chushot (14 of 16) than they did in Stok (10 of 24). Dust from the upper surfaces of house support beams were analyzed and found to contain 16 to 21% quartz. In another study of dust from the same region, Franco and Massola (1992) found dust containing 6 to 9% silica. Both authors suggest that the data reported by Norboo et al. (1991) demonstrate environmental (nonoccupational) silicosis. However, given that both Himalayan villages were agricultural and that women also are exposed to a significant amount of dust during

domestic housework, these silicosis data should be considered partially occupational, rather than strictly environmental.

Epidemiologic studies by Coultas et al. (1994), Valiante and Rosenman (1989), and Xu et al. (1993) suggest that environmental pulmonary fibrosis or environmental silicosis may be conditions in certain areas of New Mexico, New Jersey, and China, respectively. Coultas et al. (1994) conducted a prevalence and incidence study of Bernalilio County, NM (1990 population of 480,000), which was surveyed for the risk of interstitial lung disease. Pulmonary disease determinations were obtained from hospital discharge and physician referral records, histopathology reports, death certificates, and autopsy reports from October 1, 1988, to September 30, 1990. The most common diagnosis of interstitial lung disease cases of either sex were pulmonary fibrosis and idiopathic pulmonary fibrosis, which together accounted for 46.2% of all interstitial lung disease among males and 44.2% among females. The authors reported finding eight prevalent and six incident cases of "occupational or environmental" silicosis (to which mining is the likely cause); 43 prevalent and 28 incident cases of chronic pulmonary fibrosis; 58 and 63 prevalent and incident cases of idiopathic fibrosis, respectively; and 29 prevalent and 20 incident cases of interstitial lung disease not otherwise specified. The authors reported that the prevalence of pulmonary fibrosis and idiopathic pulmonary fibrosis was 29 per 100,000 for males and 27 per 100,000 for females, levels about five times greater than previous estimates (Coultas et al., 1994). The reported elevated levels of lung disease may be related to ambient dust exposures.

A surveillance system developed by Valiante and Rosenman (1989) identified approximately 60 individuals per year in the state of New Jersey with the diagnosis of silicosis for the years 1979 through 1987. More than 95% of those identified were through hospital discharge or death certificate records. Thus, it is likely that these investigators identified a higher percentage of severe cases than did Coultas et al. (1994), who also examined physician referrals and autopsy data. Still, Valante and Rosenman's estimate of annual cases was nearly one-quarter of the entire national estimate reported by the U.S. Department of Labor for a comparable time frame (U.S. Department of Labor, 1983). Extrapolating their data to the entire country, Valante and Rosenman predicted that 1,500 individuals would be diagnosed as silicotic each year. Given the gross nature of their diagnostic method and the reported hospital discharge data for New York and California (>100 silicotics designated per year from each state), the actual national number is

likely to be higher. Valiante and Rosenman were able to evaluate "completed work histories" for 278 of the 401 silicosis cases they identified for the 1979-to-1987 period. Fifteen of the 278 individuals, or approximately 5%, "had no obvious source of exposure from their work histories," suggesting the existence of an environmental impact or incomprehensive reported work histories.

Xu et al. (1993) used chest radiographs, cellular classification from bronchial lavage fluid, and biopsies to assess nonoccupational siliceous pneumoconiosis in the Minghua Desert of Gansu Province, China. The authors reported environmental dust measurements and histopathology of camel lungs in a prevalence study of two dusty communes and a control commune. Xu et al. (1993) surveyed 395 persons in Minghai and Lianghua communes, where winds and dust levels were high, and surveyed 88 subjects in Qiawtan, the control location. Dust samples were taken three times per day during April 1991 (the windy season). Details on the sampling methods for environmental dust measurements were not provided. The average dust levels ranged from 8.25 to 22 mg/m^3 at the dusty sites, whereas they ranged from 1.06 to 2.25 mg/m^3 at the control commune. Silica ranged from 15.5 to 26.1%, and between 12.5 and 21.5% of the particles were between 2 and 5 μm diameter. At the dusty site, 28 cases of siliceous pneumoconiosis were found among 395 subjects, producing a prevalence of 7.09%. Based on Chinese national pneumoconiosis criteria, there were 18 cases of Stage I fibrosis; seven cases of Stage II, and three cases of Stage III, with a clear effect of age in the distribution of the disease. No cases were found in the control population. Evidence of silicosis was found in the lung tissues of a 20-year-old camel, though none was detected in a 4-year-old camel.

There are some other reports of silicosis among domesticated grazing animals, including horses, water buffalo, and camels (Roperto et al., 1995; Schwartz et al., 1981; Berry et al., 1991). The relevance to humans of these findings in grazing animals is not clear. However, these cases, which are based primarily on veterinary clinical observations, suggest that some potential exists for environmental silicosis to human populations.

"Environmental silicosis" is not a well-defined entity. Nevertheless, the case study literature and a modest amount of epidemiology research (Valiante and Rosenman, 1989; Saiyed et al., 1991; Coultas et al., 1994; Xu et al. 1993) suggest that clarification of this term deserves consideration. The findings of Coultas et al. (1994) suggest that, in New Mexico, there is environmental interstitial lung disease, rather than silicosis per se. The 5% of identified silicotics for which Valiante and Rosenman (1989) could not identify occupational silica exposure may be

due in part to environmental, nonoccupational exposure. In China and in the Himalayas, there is evidence of radiographically defined desert pneumoconiosis (Saiyed et al., 1991; Xu et al., 1993). Given the poor sensitivity (39%) of chest X rays as a diagnostic tool when investigators are looking for this disease (Hnizdo et al., 1993), it is possible that low levels of environmental silicosis may have been overlooked in the general population, particularly in dusty, arid regions of the country.

5.4 EPIDEMIOLOGY OF CHRONIC SILICOSIS DEMONSTRATING DOSE-RESPONSE

Recent, longitudinal retrospective cohort studies of South African gold miners (Hnizdo et al., 1993; Hnizdo and Sluis-Cremer, 1993) and Ontario hardrock miners (Muir et al., 1989a,b; Verma et al., 1989) used similar statistical models to assess the relationship between cumulative silica exposure and the risk of silicosis. These studies and the studies by Rice et al. (1986) of North Carolina "dusty trades" workers and by Ng and Chan (1994) of Hong Kong quarry workers are considered key studies with respect to the quantitative assessment of silicosis risk. These and other supporting studies are described below. Their similarities and differences and an assessment of their implications for the determination of crystalline silica's quantitative, noncancer risk are discussed further in Chapters 7 and 8.

Silicosis has been recognized for decades as a serious labor hazard for South African gold miners. So much so, that today almost 85% of all South African gold miners have an autopsy at which the presence and degree of silicosis is established pathologically for compensation and research purposes. As a result, Hnizdo et al. (1993) were able to investigate the correlation between radiological and pathological diagnosis of silicosis among white miners, whose records are more complete historically than are those of other races. A total of 988 miners qualified for the study, and radiographs were available for 984 miners. Either zero or an insignificant number of silicotic nodules were found at autopsy in 658 miners. Slight, moderate, or marked silicosis was found macroscopically and histologically at autopsy in the remaining 326 miners. A systematic sample of 231 miners (1/3) was selected from the 658 miners who did not have silicosis at autopsy. Thus, a total of 557 radiographs were read in random order by three readers using ILO Category 1/1 as a positive X-ray diagnosis.

The results of this unique comparative analysis illustrate the potential problems with reliance on X-ray diagnosis of silicosis alone. Although radiographic findings resulted in only 1 to 4% false positive readings, false negatives were quite high. Even the reader whose X-ray classifications correlated best with autopsy findings did not diagnose silicosis in 75, 54, and 26% of the cases that were subsequently categorized at autopsy as slight, moderate, and marked silicosis, respectively. The average time between the date of last X ray and death was 2.7 years. Hnizdo et al. (1993) showed that the probability of a false negative reading increased with increasing years of gold mining and the average concentration of respirable dust. They also showed that there was a general agreement on the false negative evaluations between readers 1 and 2, indicating that false negatives were not due to reader error. Further indication that these discrepancies are not likely due to reader error comes from the fact that, prior to the advanced stage of silicosis, animal studies (Kutzman, 1984) also show a lack of concurrence between X-ray and histopathologic indicators of silicosis.

Using ILO profusion Category 1/1 as a cutoff and results from reader 1 (the reader whose classifications correlated best with autopsy results), the sensitivity, or the probability of a positive X-ray reading, given that silicotic nodules were found at autopsy, was 0.39, and specificity, or the probability of a negative X-ray reading, given no silicotic nodules at autopsy, was 0.99. In other words, roughly 61% of true silicotics were undiagnosed, and just 1% of the healthy nonsilicotics were diagnosed as having silicosis, using X-ray analysis of reader 1 alone and the 1/1 categorization cutoff point. Thus, Category 1/1 does not appear to be a very sensitive cutoff point for diagnosis of silicotic nodules, although it is highly specific. Hnizdo et al. (1993) recommend the use of ILO profusion Category 1/0 for a positive diagnosis of silicosis in miners who worked in low dust occupations.

One reason for this lack of sensitivity suggested by Hnizdo and colleagues is the current ILO classification guidelines (International Labour Organization, 1980) for the diagnosis of silicosis. The ILO classification does not include "linear markings" because, by definition, a diagnosis of silicosis requires the presence of nodulation, and linear markings can be produced by many factors other than inhalation of silica dust. This research and other studies (Theron et al., 1964; Craighead and Vallyathan, 1980) have observed cases where no visible nodules were diagnosed radiologically, yet a marked degree of silicosis was found at autopsy. In earlier studies of dusty trade workers, linear markings were included in the classification of silicosis, resulting in

a sensitivity level of 0.83 (Theron et al., 1964). When only the categories that indicated the presence of nodulation were included in the South African study, the sensitivity became 0.56 (Hnizdo et al., 1993).

In a retrospective cohort study, Hnizdo and Sluis-Cremer (1993) investigated the risk of silicosis among 2,235 white South African gold miners. This cohort had been selected during the years 1968 to 1971 for a study of respiratory disease (Wiles and Faure, 1977). The selection criteria were attendance at a compulsory medical examination during this period, workers' age 45 to 54 years, and underground service of at least 10 years, with less than 2 years of service in mines other than gold mines. The miners had an annual radiological examination while employed, and most returned for occasional radiological examinations after leaving the mines. As previously discussed, Hnizdo et al. (1993) used the records of 984 white South African gold miners who had died and were autopsied to determine the correlation between radiological and pathological diagnosis of silicosis. Of the remaining 1,251 miners who either died without having an autopsy or were still alive, there were 657 miners who were compensated in life for pneumoconiosis, pulmonary tuberculosis, and chronic obstructive lung disease, and there were 594 miners who were not compensated in life. Silicosis among South African gold miners is compensable if profusion of rounded opacities reaches the ILO profusion Category 1/0. A large portion of those compensated were for chronic obstructive lung disease, not specifically silicosis.

Radiographs of the following groups of miners were read in order to identify the year of onset of silicosis.

Group 1. 326 miners found to have silicosis at autopsy.

Group 2. 231 miners systematically selected from the 658 who did not have silicosis at autopsy.

Group 3. 657 miners who had compensable lung disease in life.

Group 4. 100 miners from the 594 who did not have compensable disease in life.

The onset of silicosis was defined as the year in which rounded opacities of ILO Category 1/1 or higher were first read. Only the reader whose readings correlated most strongly with the autopsy findings was used for further analysis (Hnizdo et al., 1993).

In the study by Hnizdo and Sluiz-Cremer (1993), exposure levels were assigned to 11 occupational categories based on measurements taken with a thermal precipitator in the late

1950s and in the early 1960s in 20 gold mines (Beadle and Bradley, 1970). The amount of incombustible and acid-insoluble dust particles (mainly quartz and silicates) was measured in terms of the surface area of the respirable dust and the number of respirable (sizes 0.5 to 5.0 μm) particles per cubic meter (after both acid and heat treatment). Cumulative dust exposure in milligrams per cubic meter years was calculated for workers using data for mean mass respirable dust concentrations for various activities within mines, number of dusty shifts, and average number of hours spent underground. The respirable dust in South African gold mines was found to contain about 30% silica within the airborne dust. Net number of years working in dusty occupations in gold mines was calculated as the total number of dusty shifts divided by 270 (average number of shifts per year).

Figure 5-1 shows the estimated cumulative risk of silicosis in relation to the cumulative dust exposure. Of the 2,235 miners, 313 developed radiological evidence of silicosis (ILO Category $\geq$ 1/1). The onset of silicosis occurred at an average age of 56 years, after 27 years of net service. For 135 of the 313 miners (43%), the onset occurred while the miners were still working in the mines, at an average age of 51 years (range 39 to 61 years). The other 178 miners (57%) developed silicosis an average of 7.4 years (range 0.1 to 25 years) after leaving the mines, at an average age of 59 years (range 44 to 74 years). Thus, a large portion of the miners developed silicosis after 50 years of age and after their employment ended.

An epidemiological investigation to determine the relationship between silicosis in hardrock miners in Ontario and cumulative exposure to silica dust has been reported (Muir et al., 1989a,b; Verma et al., 1989; Muir, 1991). The data for this study were derived from three principal sources: (1) full-sized chest radiographs taken annually on all miners after 1927 and before 1959 and semi-annually after 1959; (2) dust measurements obtained by using konimeters; and (3) employment records specifying mine, job, and start dates. Twenty-one mines were found to possess adequate records and formed the focus of the study. The cohort consisted of 2,109 miners first exposed between 1940 and 1959 who spent 80% or more of their total mining experience in one or more of the designated 21 mines.

All chest X rays of the 2,109 men were assembled and classified by five readers. Based on an initial screen of the two most recent chest X rays from each miner, the films of 650 miners required further scrutiny. Each of five readers separately classified all six zones of the lung fields

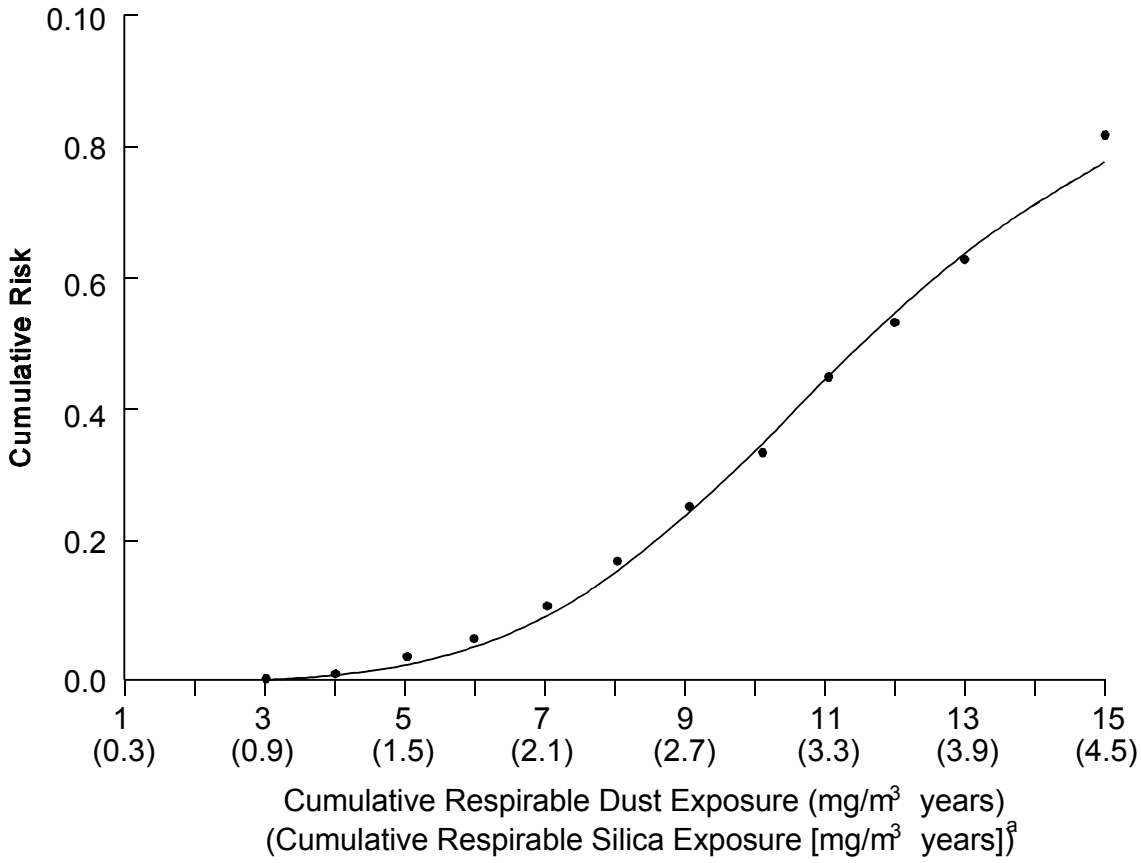

Figure 5-1. Cumulative risk of silicosis in white South African gold miners versus cumulative respirable dust and silica exposure. Miners were followed from 1968 or 1971 to 1991.

[a]Assumes respirable silica is 30% of respirable dust levels.

Source: Hnizdo and Sluis-Cremer (1993).

according to the prevalence and type of opacity by using ILO standard reference films (International Labour Organization, 1980). When two or more readers classified any one of the zones as 1/1 or greater for small opacities, all films of that miner were selected for further evaluation (Muir et al., 1989a).

Exposure measurements in the mines studied by Verma et al. (1989) had been taken over more than 40 years (from 1940 to 1982) with konimeters and expressed in particles per cubic centimeter of air. An extensive, side-by-side comparison of the konimeter and gravimetric sampling was initiated to derive a konimeter/gravimetric silica conversion curve. A total of 2,360 filter samples and 90,000 konimeter samples were taken over 2 years in two mines, both in

existing conditions as well as in an experiment in which dry drilling was used to simulate the high-dust conditions of the past. The conversion relationship established was nonlinear and may reflect the limitations of the konimeter in measuring high dust concentrations and of the gravimetric respirable sampler in measuring low dust concentrations. Different relationships were established for gold and uranium mines, that may be due to different fractional silica concentrations in the host rock. Konimeter counts were converted to gravimetric respirable silica equivalents. Cumulative respirable silica dose for each miner was calculated by linking the gravimetric concentrations for each combination of year, mine, and task with the miner's detailed work history.

Of the 2,109 Ontario hardrock miners, only 32 were considered by one or more readers to have silicosis (ILO Category $\geq$ 1/1). A great deal of interreader variability was apparent. One of the five readers identified just seven silicotic cases. Consensus among readers with respect to identification of silicosis was reached on only six cases, and never did the readers reach complete consensus with respect to age of the individual at diagnosis. Because of the low frequency of silicotics identified in this study, the data were fitted to parametric failure-time models and assigned confidence intervals. Because it generally is accepted that there is a delay between the time of deposition of silica in the lungs and the appearance of silicosis, the data were analyzed using 0-, 2-, and 5-year exposure lags. For each case, the cumulative dose up to the time of diagnosis (or the time the individual left the industry) was calculated, less the dose accumulated during the last 0, 2, or 5 years. The 5-year lag consistently provided the best fit to the data (i.e., largest log-likelihood value). Figure 5-2 shows the fitted Weibull model for each reader showing the estimated cumulative risk of silicosis in relation to the cumulative dust exposure (milligrams per cubic meter years), lagged 5 years.

For the 32 miners determined to be silicotic by one or more readers, the onset of silicosis occurred at an average age of 52 years, after an average of 26 years of net service. The onset of silicosis was identified only while the miners were still working in the mines. A radiological survey of retired miners was not performed. While employed in the mines, many of the miners had inhaled finely divided aluminum dust prior to underground work, as a prophylactic measure. Muir et al. (1989b) expressed concern that, once retired, "...cessation of aluminum therapy could have led to unmasking of silicotic lesions...."

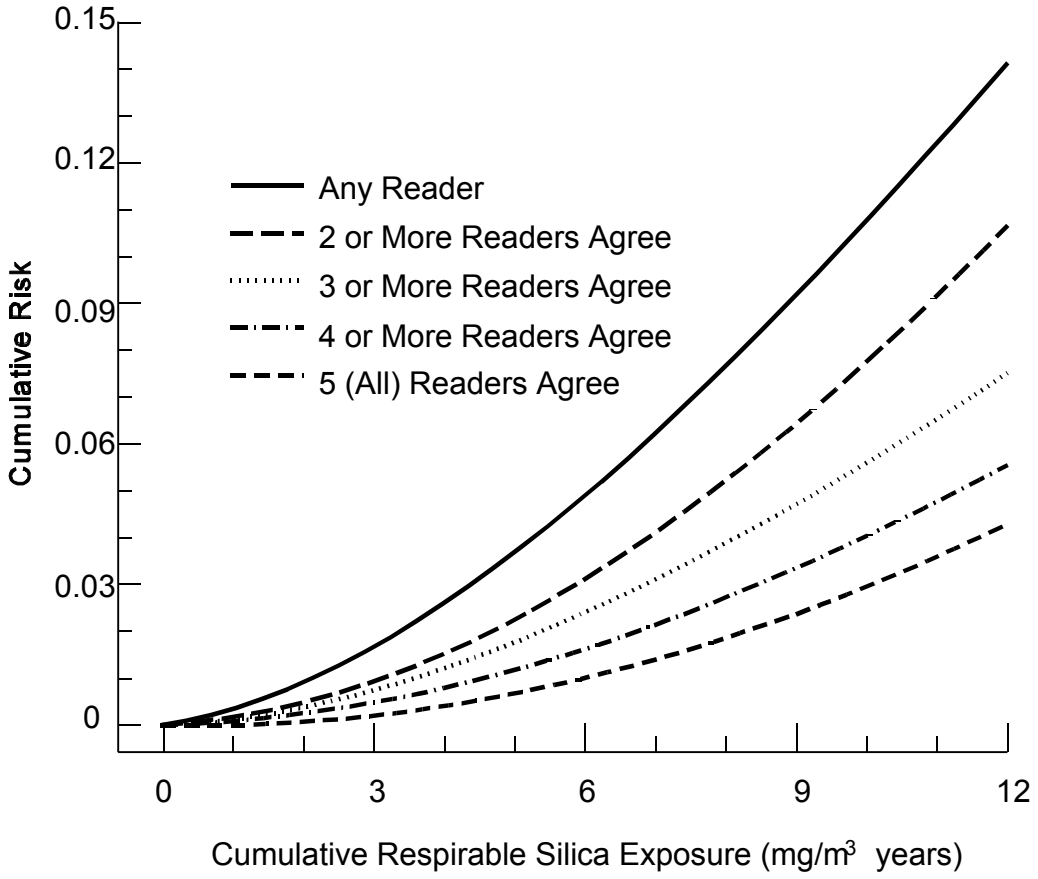

Figure 5-2. Cumulative risk of silicosis in Canadian hardrock miners versus cumulative respirable silica exposure, lagged 5 years. Fitted Weibull models show various levels of reader consensus.

Source: Muir et al. (1989b).

As indicated by the authors, their data alone do not provide a method of identifying a "best" reader. Assuming, however, that the sensitivities and specificities observed for readers in the Hnizdo et al. (1993) study are applicable, the findings of readers 2 and 3 would most likely correlate best with autopsy results because they identified twice as many cases as associate readers. The analysis in Chapter 7 is based on the results from these two readers.

McDonald and Oakes (1983) analyzed a cohort of 1,321 South Dakota gold miners employed for at least 21 years prior to 1965, with follow-up through 1973. Average exposures were estimated based on observed dust counts from 1937 to 1973. The investigators identified 49 cases each of silicosis and turberculosis from death certificates. They estimated the risk of dying from silicosis or tuberculosis (as the underlying cause of death) by category of average

exposure. They found an increasing linear trend in risk of about 2.4% for each 0.1 mg/m^3 of silica exposure. They did not calculate risk by cumulative exposure. More recently, Steenland and Brown (1995b) estimated the risk of silicosis by cumulative exposure-years in an expanded cohort of 3,330 South Dakota gold miners who had worked at least 1 year underground between 1940 and 1965 (average 9 years), with follow-up through 1990. During 106,000 person years of observation, 1,551 of the 3,330 miners died. Only 2% of the cohort was lost to follow-up. To convert from observed dust count to milligrams per cubic meter, the relationship 10 mppcf = 0.1 mg/cm^3 was used. Average dust exposures for six job categories were estimated using existing measurements for each year from 1937 to 1975. Exposures prior to 1937 were estimated at 25 mppcf by industrial hygienists familiar with early mine conditions. Although the mines continued to operate after 1975, exposure levels were low and only 14% of the cohort were still employed. Thus, the lack of exposure data beyond 1975 resulted in modest underestimate of cumulative exposure. The cohort was exposed to a median silica level of 0.05 mg/m^3 (0.15 mg/m^3 for those hired before 1930). Using death certificates and two cross-sectional radiographic surveys (636 cohort X rays in 1960, 229 cohort X rays in 1976), the authors determined 170 cases of silicosis. Silicosis rates (cases per person-time at risk) were estimated for seven cumulative exposure categories, stratified by 5-year age and calendar-time intervals. Crude rates then were adjusted for age and calendar time using Poisson regression. Although both age and calendar time were highly associated with exposure (i.e., older workers with earlier exposure had higher cumulative exposure), they would not be expected to confound an exposure-response analysis because, unlike many other chronic diseases, silicosis has no background rate for nonexposed populations that changes with age or calendar time. The empirical increase in silicosis rates with age and the substantial impact of calendar time reported by Steenland and Brown (1995b) may be the result of deficient historical information on exposures or because age and calendar time serve as surrogates for dose. Figure 5-3 shows the estimated cumulative risk of silicosis in relation to the cumulative respirable silica exposure with and without adjusting for age and calendar time. The unadjusted risk of silicosis was determined to be less than 1% for a cumulative respirable silica exposure under 0.5 mg/m^3 years, increasing to 68 to 84% for the highest cumulative exposure category of more than 4 mg/m^3 years. Steenland and Brown (1995b) estimated a lifetime risk of silicosis for someone exposed for 45 years at the Occupational Safety and Health Administration (OSHA) standard (0.09 mg/m^3) to be 35 to 45%, after adjusting

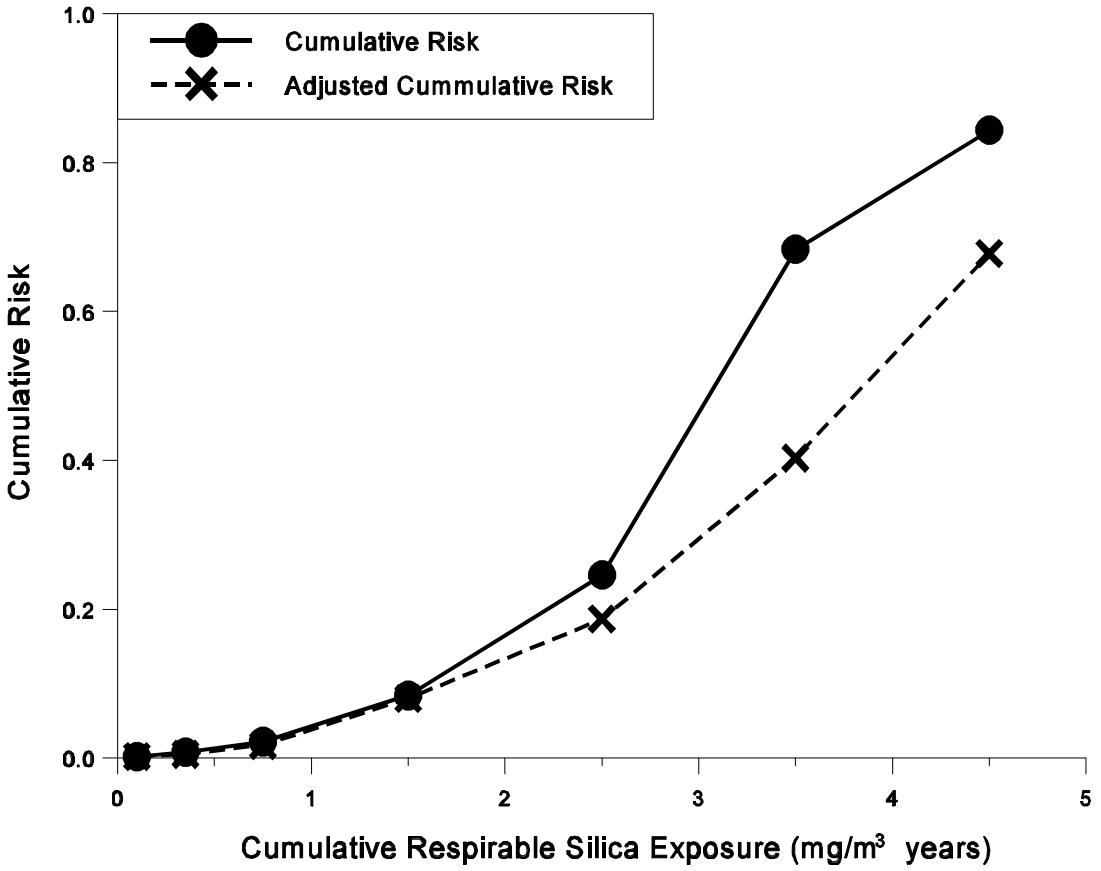

Figure 5-3. Cumulative risk of silicosis in South Dakota gold miners versus cumulative respirable silica exposure. Miners were followed from 1940 to 1991.

Source: Steenland and Brown (1995b).

for competing causes of death. As can be seen from Figure 7-1, these cumulative risk estimates are more consistent with the findings of Hnizdo and Sluis-Cremer (1993) than with the observations of Muir et al. (1989).

An exposure-response relationship was seen in a case-control study with North Carolina dusty trade workers exposed to silica in a wide range of industries, such as mineral mining and milling, quarrying of granite and crushed stone, hardrock mining, and foundry work (Rice et al., 1986). Both cases and controls were ascertained from a program of environmental and medical surveillance of industries with silica-exposed workers maintained by the State of North Carolina since 1935. Working lifetime exposures to quartz were estimated for 216 male workers with silicosis and 672 disease-free workers. Both silicotics and controls still were actively employed

when their disease status was ascertained; some unknown proportion of controls may have been cases after leaving employment. Impinger data (counts from samples collected by program industrial hygienists) were combined according to commodity-specific, time-weighted average (TWA) formulae; mass data (from samples collected with a mass-respirable cyclone) were converted to count estimates by dividing by 0.09 (0.09 mg total respirable mass/m^3 = 1 mppcf). The cumulative quartz exposure was expressed as million particle years (mpy). The worker exposures were categorized into four groups: exposure <20 mpy was considered the reference group, and the range of exposures in the other categories were 20.0 to 59.9, 60.0 to 179.9, and ≥180 mpy. Using several independent methods of analysis, the investigators calculated that a statistically significant (p value not provided) risk of silicosis was present at an average cumulative exposure of 98 mpy, but not at 37 mpy. The authors also estimated that, over a 40-year working period, these values would correspond to approximately 250 and 100 μg/m^3 (2.5 and 1 mppcf), respectively, with the lower value equivalent to the current OSHA standard for dust containing 100% quartz. Smoking history was not found to substantially affect the results. Although this study appears to identify a relationship between exposure and response, questions regarding the quality of early X-ray diagnosis and the existence of confounding exposures limit the study's use in a risk assessment. Of the 216 identified cases, nearly half (101) were in Group 0, the reference group. One explanation for this might be reader misclassification. Based on median readings of three "B" readers using 1980 ILO procedures (International Labour Office, 1980), 44% of the radiographs classified as silicotic between 1935 and 1983 by the North Carolina Advisory Medical Commission were more recently reclassified as either nonsilicotic (Category 0) or unreadable (Amandus et al., 1992). Although there is no way to project accurately the impact of this finding on the Rice et al. (1986) study, it is reasonable to assume that most of these misclassifications would have been for slight cases of silicosis, which more likely would be associated with the reference group than with the higher exposure groups. Thus, the reference group from the Rice et al. (1986) study is likely to contain false positives. This potential for false positives in the reference group places some doubt on the designation of the low exposure group (37 mpy) as a no-observed-adversed-effect level (NOAEL). Further, workers in this study were selected from a broad spectrum of occupations and were exposed to different combinations of minerals, including mica, talc, and kaolin.

Ng and Chan (1994) evaluated the risk of radiological opacities among 338 male Hong Kong granite workers employed a minimum of 1 year between 1967 and 1985 (Ng and Chan, 1994). Films were read independently by three physicians using International Labour Organization (1980) criteria. The authors estimated past cumulative silica exposures from quarry- and job-specific airborne dust (midget impinger) samples, with an overall average of 27% silica. The workers' cumulative samples were converted to gravimetric equivalents of respirable quartz, and each worker's dust score was obtained by multiplying the median concentration by years worked for each job, and summing over calendar years. Details of the exposure assessment for this work are described in a previous report (Ng et al., 1989). Rounded or irregular opacities of profusion 1/1 or greater were defined as silicosis if they were so read by two of the three readers. The probability of radiological abnormalities increased for men 50 years and over, according to their cumulative dust exposure, and no smoking effect was shown. Linear and logistic models both showed risks of 6% rounded opacities, and 8% irregular opacities for an average 50-year-old worker with cumulative silica exposure of 2.0 mg/m^3 years. The authors suggest a threshold exposure of <1.0 mg/m^3 years may be compatible with zero risk, because no cases of X-ray silicosis were detected. This is in general agreement with the results of Hnizdo and Sluis-Cremer (1993) and Muir et al. (1989b), which also suggested zero risk at cumulative silica exposures below 1 mg/m^3 years. Ng and Chan also discussed the possible effects from exposure bias and survivor bias and their effect on the risk extrapolations. Although the study included workers who previously were exposed but who had left the industry, thereby accounting for development of silicosis after employment, researchers examined only survivors of the original cohort. Among 53 men known to have died, 17 were stated to have died of silicosis. Further, the ex-workers were self-selected, thereby creating a bias towards those in the surviving group that felt they had received significant dust exposure. For these reasons, Ng and Chan (1994) may have underestimated the risk to high-exposure groups and overestimated the risk to low-exposure groups.

5.5 OTHER STUDIES OF SILICA-EXPOSED WORKERS

This section reviews studies, including silicosis morbidity and mortality research, in which concentration-response findings were supportive, but alone could not form the basis for a health-

effects benchmark. Although these studies provide important adjunct information, they were generally designed for purposes other than the development of a concentration-response relationship.

The incidence of silicosis in Vermont granite shed workers has been analyzed by a number of investigators. In the earliest report, Russell et al. (1929) studied 972 granite shed workers and divided them into four exposure groups according to the average "dustiness" in the work environment: (1) 3 to 9 mppcf (108 workers), (2) 20 mppcf (146 workers), (3) 27 to 44 mppcf (104 workers), and (4) 37 to 59 mppcf (614 workers). Dust samples contained an average of 35% crystalline silica and a number of silicate minerals. The years of employment ranged from <5 to ≥35 years, with 75% of all workers employed for 10 years or more, and, grouped by increasing order of dust exposure, 36, 31, 59, and 55% of workers were employed for 20 years or more. Diagnosis of silicosis was based on exposure history and physical examinations, corroborated by chest X rays in a number of cases. The most frequently observed symptoms were unproductive cough, dyspnea, pains in chest, and changes in breath sounds and fremitus. In the group with highest silica dust exposure (37 to 59 mppcf), the first case of silicosis appeared after 2 years of employment. All 614 workers in this group developed at least an early stage of silicosis after 4 years of employment. The first case of more advanced silicosis appeared after 5 years, and after 9 years, approximately 90% of workers had advanced to this stage. In the groups exposed to 20 or 27 to 44 mppcf, the development of silicosis was reportedly proportional to silica dust exposure (number of cases not discernible from data presented). In the lowest exposure group (3 to 9 mppcf), two cases of early silicosis appeared after 10 years, and one case of moderately severe silicosis appeared after 6 years of exposure.

Institution of dust control measures in 1937 resulted in a reduction of silicosis among Vermont granite workers (Ashe and Bergstrom, 1964). In 1969, the Harvard School of Public Health and the Industrial Hygiene Division of Vermont conducted a comprehensive study of the relationship between exposure to granite dust, percent quartz content of the dust, and lung disease among granite shed workers exposed for many years to low levels of granite dust. The results of the study were reported in three articles by Theriault et al. (1974a,b,c); a 4-year follow-up study was reported by Musk et al. (1977). A cross-sectional survey was carried out on a group of 883 workers between the ages of 25 and 65 who were working in the granite sheds. Chest X rays and their relationship to lifetime dust exposure, ventilatory function, and smoking habits were

examined. Cumulative dust exposures were calculated for each worker as the number of years of exposure at an average granite dust concentration of 523 $\mu g/m^3$ and an average quartz (respirable silica) concentration of 50 $\mu g/m^3$ and expressed as dust years. The fractional silica concentration of the respirable dust was about 9% in more recent years and 13 to 17% in the early years (Theriault et al., 1974a).

Chest X rays were obtained from 784 workers and classified by a single reader according to UICC/Cincinnati classification for pneumoconiosis; 551 (70%) of the radiographs were considered normal, and 233 (30%) showed various types of lung opacities that were divided into subgroups according to shape (rounded or irregular), size, and profusion (number of opacities per unit area). Workers with abnormal radiographs were exposed, on average, to 2.3 times more dust years than those with negative radiographs (43 dust years versus 19 dust years). The irregular opacities correlated with age and cigarette smoking, but not with cumulative dust exposure. The size and profusion of the rounded opacities correlated to increasing dust exposure and were considered to be indicative of silicosis in 45 (19%) of workers with lung opacities. Based on a plot of workers with abnormal radiographs against dust years (at a dust level of about 50 $\mu g/m^3$ as crystalline silica), about 30% of the workers showed silica-related lung opacities at exposures of 0 to 35 dust years. After that, the curve increased dramatically: at 55 dust years, 60% of granite shed workers had opacities. Theriault et al. (1974c) estimated that 46 dust years of exposure would produce lung opacities in 50% of the workers (the specific distribution of the number of silica-related cases by dust year was not reported). However, because 67 (39%) of the abnormal films showed irregular opacities that were not correlated with dust exposure, it might provide some estimate of the true dust effect to assume that the films with irregular opacities were distributed randomly in each dust category. On this basis, Muir et al. (1989b) estimated the true probability of developing Category 1 pneumoconiosis after 46 years of exposure to 0.05 mg/m^3 of respirable silica (cumulative exposure of $46 \times 0.05 = 2.3$ mg/m^3 years) to be 30%.

The Theriault et al. (1974a,b,c) studies have received criticism from other authors (Graham et al., 1981; Morgan, 1975) and NIOSH (National Institute for Occupational Safety and Health, 1975). The main concerns are that the chest X-ray films were examined by only one physician who was not certified by NIOSH as a "B" reader, and the fact that 30% of the workers identified with silicosis had no apparent dust exposures. Graham et al. (1991) carried out a subsequent radiographic survey of the Vermont granite industry. They also examined the chest X rays of

quarry and stone shed workers who had been exposed since regulatory controls reduced dust levels in 1938 to 1940. The films were read by three "B" readers, using the International Labour Organization (1980) classification system. An abnormal X-ray was defined when either two or all three of the readers assigned a profusion score of 1/0 or greater to the film, identifying abnormalities consistent with pneumoconiosis, either of the rounded or irregular type. Using these criteria, Graham et al. (1991) identified just seven of 972 (0.7%) radiographic abnormalities consistent with silicosis. They used these data and their estimation that average crystalline silica exposures were 60 $\mu g/m^3$, with 12% of the samples exceeding 100 $\mu g/m^3$, to conclude that dust controls essentially had eliminated silicosis. A major problem with this assertion is that the cohort consisted predominantly of middle-aged men (42 ± 13 years), whereas silicosis has been observed in other studies (Ng and Chan, 1994; Hnizdo et al., 1993; Steenland and Brown, 1995b) to be a disease that primarily impacts the older workers, with the average age of silicosis onset being consistent over a broad exposure range at approximately 56 years (Hnizdo et al., 1993). Consistent with this observation is the fact that the average age of the 28 workers determined to be silicotic by Graham and colleagues was 54 ± 9 years, markedly higher than that which was reported for all participants (42 ± 13 years) and for workers without abnormal X rays (also reported to be 42 ± 13 years). Although, Graham et al. (1991) reported that the risk of silicosis significantly increased with years worked in granite ($p = 0.022$), they, and previous studies of Canadian (Muir et al., 1989a,b) and North Carolinian (Rice et. al., 1986) dusty trade workers, did not ascertain the potential for silicosis to develop beyond retirement. This potential for progression after the cessation of exposure has now been documented in both human (Hnizdo et al., 1993; Steenland and Brown, 1995b) and laboratory animal (Kutzman, 1984a,b) studies. Further compounding the uncertainty associated with this lack of follow-up beyond retirement is an apparent self-selection bias for younger employees with fewer years employment in the granite industry. Graham et al. (1991) reported that "those who participated [972 workers who had X rays taken] appear to be younger [42 ± 13 years versus 46 ± 13 years] and to have worked for fewer years in the granite industry [18 ± 12 years versus 20 ± 13 years]" than a group of 239 employees who participated in other health evaluations but did not obtain X rays. (An additional group of 161 workers that did not participate in any form of health evaluation were not included in this analysis.) In addition, Graham et al. (1991) could provide only a crude estimate of average

exposures across all job categories and were not able to calculate individual worker exposure estimates as was done in the Canadian, North Carolina, and South African studies.

Vermont granite workers with abnormal radiographs exhibited decreased forced vital capacity (FVC), forced expiratory volume at 1 s (FEV_1), and total lung capacity (TLC), but not residual volume. Residual volume increased with smoking but not with dust exposure, indicating obstructive lung disease conditions. Of these 784 workers, 668 remained in jobs in which their exposure to granite dust continued and were examined for changes in pulmonary function 4 years later (Musk et al., 1977). Musk and co-workers reported a further decrease in FVC of between 0.07 and 0.08 L/year and a similar reduction of FEV_1 of between 0.05 and 0.07 L/year over the course of the follow-up period. This decline is about twice that expected per year as adults age (U.S. Environmental Protection Agency, 1994a). However, Graham et al. (1981) reported that the losses of pulmonary function in these same granite workers were not detected in 1979, when 487 workers were retested. This discrepancy was attributed to inaccuracies associated with the previously reported spirometric data (Graham et al., 1981). Graham et al. (1994) reexamined the loss of FVC and FEV_1 in Vermont granite workers over the course of the next 8 years, from 1979 to 1987. The mean age of the workers was 42.9 years, and the mean years employed was 19.3 years. The investigators did not detect pulmonary function loss in this cohort after adjusting for age, height, and smoking status.

Davis et al. (1983) compared mortality records of 969 white male Vermont granite workers with that of U.S. white males (1952 to 1978). An estimate of lifetime granite dust exposure was obtained for each individual by combining industrial hygiene information with work histories. Trends of increasing mortality from silicosis and tuberculosis with increasing lifetime exposure were observed. Only one of the 28 silicosis deaths occurred among the men who were hired after dust controls were implemented in the granite industry. The highest concentration of granite dust observed during that postcontrol period without detecting a death from silicosis was 67.5 $\mu g/m^3$. The 67.5-$\mu g/m^3$ exposure level for workers exposed between 1937 and 1978 (maximum of 41 years) may be considered a NOAEL for silicosis mortality from occupational exposure to silica.

The NIOSH conducted a study at two silica flour mills (producing finely powdered crystalline silica) to determine the prevalence of silicosis in workers and to survey airborne silica dust concentrations (Banks et al., 1981; National Institute for Occupational Safety and Health,

1981). The medical evaluation consisted of a chest radiograph, spirometry, and a questionnaire emphasizing medical history and respiratory symptoms. Based on the ILO classification of chest radiographs for pneumoconiosis, the study found that, of 61 current and former workers with 1 to 14 years of exposure to silica dust, 16 (26%) had chest radiographs consistent with silicosis, and 7 (11%) had PMF (National Institute for Occupational Safety and Health, 1981). The average duration of exposure to silica dust for the 16 workers with chronic silicosis was 7.7 years; the 7 workers with PMF of the lungs had an average exposure duration of 7.1 years. One worker (age 24) had progressive massive fibrosis after only 2.5 years of silica exposure, another after 4 years, and two others after 6 years. The silica content of the dust from both mills was 99% crystalline silica; the mean diameters of the dust particles from air samples at various mill operations were within the respirable range (2.3 to 5.2 μm). Of 91 personal dust samples collected, 77 were above NIOSH's recommended standard of 0.05 mg/m^3 for respirable crystalline silica (Banks et al., 1981; National Institute for Occupational Safety and Health, 1981).

Ng et al. (1985) described five independent case reports of silicosis among jade workers in Hong Kong exposed to silica flour in the polishing process. The disease had an early onset and was rapidly progressive in three patients after an occupational exposure of 5 to 10 years; one patient showed evidence of tubercular infection in addition to silicosis. In another patient, nephritis and renal failure were seen together with progressive massive fibrosis. Measurements of the airborne dust concentrations were conducted in the work place of one patient who had worked with jade for 22 years and exhibited mild impairment of pulmonary function and silicotic lesions in the lungs (confirmed by chest radiographs). A bulk sample of the silica flour used contained 97% crystalline silica; the silica content of the collected respirable dust was 89%. Gravimetric analysis of air samples showed a TWA concentration of 1.01 mg/m^3 when an exhaust fan was running and 5.62 mg/m^3 when the fan was off. The respirable dust concentrations were 0.34 and 0.72 mg/m^3 under the same circumstances, thereby exceeding OSHA's permissible exposure limit of 0.1 mg/m^3 for respirable crystalline silica.

Ceramic industry has been a source of silicosis studies over many decades. Cavariani and colleagues evaluated radiological abnormalities (ILO Category 1/1 or greater) and cumulative silica exposure in 2,480 male Italian ceramics workers employed in the Civitacastellana region from 1974 to 1991 (Cavariani et al., 1995). Cavariani and co-workers used industrial hygiene data collected from 1989 to 1992 in the 10 largest ceramics plants in the region to estimate dust

exposures in sanitary ware production (33% silica) and pottery making (22% silica). The authors used Cox's proportional hazards models (Kaplan-Meier method) to evaluate the risks for workers with the greatest exposure to compare with workers having the least. The investigators reported that the likelihood of silicosis was 48% after 30 years employment, with 37% positive radiographic evidence at 55 years of age. The risk followed in a linear fashion with those employed 30 years or more having a hazard ratio of 14.6 compared to those employed less than 10 years, with a doubling of risk for those in sanitary ware and among smokers. Interaction terms for smoking and exposure duration were statistically significant ($p = 0.037$), although they were more than additive and less than multiplicative. The authors discussed the likelihood that their exposure estimates underestimated past silica levels by three- to fivefold (compared to the current standard of 0.1 mg/m^3), because they could study only surviving workers, whose health surveillance included chest X rays and who all were actively employed (and so omitted retirees). The investigators' findings appeared to be closer to the South African data than to the Ontario findings with regard to extrapolations (Cavariani et al., 1995).

Steenland and Brown (1995a) conducted a follow-up mortality study of a large cohort of 3,328 South Dakota gold miners from 1940 to 1990, in which 1,551 deaths occurred, and for which there were dust exposure estimates developed by NIOSH. Cohort mortality was compared with U.S. male rates using an analytical program developed by the investigators. Cumulative mean gravimetric particle levels by year and job were developed for assessing dose-response associations, and the authors evaluated the mortality risk for pneumoconiosis and other respiratory diseases (PORD). The authors reported that overall mortality for PORD produced a standardized mortality ratio (SMR) of 2.61 (95% confidence interval [CI] = 2.11 to 3.20) and, furthermore, an SMR of 1.79 for <8,000 silica dust days; for 8,000 to 32,000 dust days, the SMR was 1.46; for 32,000 to 48,000 dust days, the SMR was 2.95; and, for >48,000 dust days, the risk was 8.87 (chi-square trend test $p < 0.05$). This indicates that when comparing the PORD mortality risk at the highest silica exposure with the lowest level (<8,000 dust days), there is a fivefold variation mortality and a strong dose-response gradient in between.

Saiyed et al. (1985) conducted a medical and environmental survey in the slate-pencil industry in central India. The slate-pencil workers included 405 cutters who were directly exposed to silica dust and 117 male and 71 female workers who were exposed to silica in the general work environment (noncutters). The mean duration of employment was 7.29, 7.62, and

14.69 years for cutters, male noncutters, and female noncutters, respectively. The health survey consisted of medical and occupational histories and full chest X rays for each worker. Results of chest radiographs showed a high incidence (54.5%) of silicosis among the 593 workers examined (cutters, 60%; male noncutters, 41%; and female noncutters, 46.5%). Progressive massive fibrosis was seen in 17.7% of all workers, with detectable lung lesions appearing after relatively short exposure times (<5 years for cutters and 6 to 10 years for male and female noncutters). The mean dust levels in the respiratory zone of the cutters were 46.47 mg/m^3 (total dust) and 10.41 mg/m^3 (respirable dust) with a 56.5% crystalline silica content. The levels in the general work environment were 24.70 mg/m^3 (total dust) and 5.53 mg/m^3 (respirable dust). These levels of dust are likely to have resulted in levels of respirable crystalline silica that were well above the current OSHA permissible exposure limit of 0.1 mg/m^3.

Since the mid-1950s, Chinese occupational hygienists have been measuring and recording workers' environmental exposures to total airborne dust and to silica. Silicosis prevention programs were developed in response to reports of wide-scale problems in Chinese industries. In order to make productive use of this rich data source for epidemiological investigation of the relationship among silica exposure and silicosis and lung cancer, a collaborative investigation was begun between the Tongji Medical University in Wuhan, China, the U.S. National Cancer Institute, and NIOSH. These investigations focused on assessing the relation of the Chinese radiology reports to International Standards from ILO (Yang et al., 1991; Chen et al., 1991); developing cumulative lifetime exposure estimates from historical exposure data and documented work histories (Dosemeci et al., 1991); assessing exposure to confounding agents such as asbestos, radon, arsenic, nickel, and cadmium; and assessing airborne-dust-sampling methods and silica analysis techniques (Hearl et al., 1991; Wu et al., 1991). As part of these investigations a noncancer assessment of exposure levels and Chinese silicosis evaluations was reported by Hearl et al. (1991).

The study by Hearl et al. (1991) was designed to compare Chinese dust-monitoring strategies with those of the United States. Side-by-side monitoring, using both Chinese and U.S. dust-sampling equipment, was performed in 29 Chinese mines or factories. A comparison of Chinese and U.S. respirable dust measurements produced an overall correlation of 0.77, with a regression coefficient indicating that U.S. respirable dust measurements were approximately 28.5 ± 3.5% of the corresponding Chinese measurement, plus a 0.27 ± 0.15 mg/m^3 bias. An exposure-

response analysis was performed for 1,036 workers at the 29 facilities using cumulative lifetime exposure estimates derived from individual work histories, the facilities' dust data (Dosemeci et al., 1991), and 1986 Chinese radiographic criteria of pneumoconiosis. Workers were divided into four categories, ranking the degree of silicosis as 0^+ (suspect silicosis), 1, 2, or 3, with Grade 3 indicating the most severe levels of disease. At the lowest disease category (0^+), the mean respirable quartz level was 26.2 ± 2.6 mg/m^3 years. Assuming a 35-year working lifetime, this translates to an average daily exposure of 0.75 ± 0.07 mg/m^3 of respirable dust. Using the above correlations, the Chinese measurement could be converted to a U.S. exposure of 0.47 ± 0.05 mg/m^3 of respirable quartz.

Pang et al. (1992) conducted another retrospective epidemiology study of selected tungsten miners in China. Historical surveillance and monitoring data were collected for 1,151 workers exposed to silica dust from 1958 to 1987. Those who previously were exposed to other dusts were excluded. According to employment practices in China, the age of first exposure was assumed to be 18 years, and the duration of exposure was assumed to be 30 years. The total and respirable silica dust concentrations for major job categories were estimated from historical surveillance data, but individually linked samples were not reported. The ratio of respirable silica dust levels to total silica dust concentration was 0.529, and the estimated crystalline silica content in respirable dust averaged 24.7%. Results of multiple regression analysis showed that the probability of developing silicosis was correlated positively with cumulative exposure to silica dust (diagnostic criteria for silicosis were not provided). At an exposure concentration of 0.24 mg/m^3, the probability of developing silicosis was estimated to be 0.8% over a 30-year exposure period in the absence of tuberculosis. This study lacked experimental details regarding methods for exposure estimates and diagnostic procedures.

Thomas and Stewart (1987) evaluated the mortality risk of nonmalignant respiratory disease (rather than silicosis specifically) among pottery workers exposed to silica (quartz) and nonfibrous talc. The study population consisted of 2,055 white males who had been employed for at least 1 year between 1939 and 1966 at three plants of a single U.S. company. No measurements of airborne silica or talc dust were available; however, the investigators ranked various job categories according to their potential exposure (none, low, or high). Follow-up through January 1, 1981, indicated a substantial excess of nonmalignant respiratory diseases (pneumonia, pneumoconiosis, emphysema, and other respiratory diseases) among workers with high levels of

exposure to silica dust (54 observed deaths, 23.4 expected; SMR = 2.26). The risk of respiratory disease increased with the number of years exposed; was not enhanced by talc exposure; and decreased in more recent time periods independent of duration of exposure, suggesting the existence of improved dust controls. There was no information on smoking history.

Dental technicians are exposed to various dusts including silica, alloys, and acrylic plastics (Choudat, 1994). The prevalence of pneumoconiosis among dental technicians is very high and related to duration of exposure. Three epidemiological studies have found a prevalence of 1/0 or greater in about 15% of technicians with 20 or more years of exposure (Rom et al., 1984; Choudat et al., 1993; Tuengerthal et al., 1984).

5.6 EPIDEMIOLOGY OF OTHER SILICA-RELATED CONDITIONS HAVING DOSE-RESPONSE GRADIENTS

Tuberculosis is a well-known sequela of silicosis, and there are many examples of clear dose-response gradients for TB mortality. Because of the strong association of TB with silicosis, it will not be considered further.

The only nonsilicosis and non-TB study showing dose-response findings was the study by Steenland and Brown (1995a) who evaluated the mortality risk by cumulative silica dust exposure for chronic renal disease. The authors reported that chronic renal disease had an SMR of 0.40 for <8,000 silica dust days, for 8,000 to 32,000 dust days, the SMR was 0.34; for 32,000 to 48,000 dust days, the SMR was 1.26; and, for >48,000 dust days, the risk was 2.77 (chi-square trend test <0.05). The findings demonstrate a dose-response effect for renal disease mortality, and miners with >48,000 dust days have a 6.9-fold greater likelihood of dying than do those with the lowest exposure (<8,000 dust days).

5.7 NONSPECIFIC PULMONARY EFFECTS FROM SILICA EXPOSURE

Although the association of dust exposure and airflow obstruction initially was observed in coal miners, it now appears that sufficient exposure to many (if not all) mineral dusts, including coal, silica, asbestos, talc, mica, iron oxide, and aluminum oxide, may have similar effects. Within the last few years, it has become clear that exposure to silica and other mineral dusts is associated

with abnormalities in the small airways, manifested in humans and animals as emphysema or airflow obstruction (Wright et al., 1992). The specific morphologic features and functional changes have been reviewed extensively by Wright et al. (1992) and Becklake (1985, 1989a,b). The following is a discussion of studies that have identified these effects in either humans or animals and the relevance of these effects to a silica health-risk assessment.

5.7.1 Emphysema

There appears to be a common pattern of response to mineral dust within the small airways. The nature of the dust may be of less importance for the induction of emphysema response than the amount of dust deposited. Although the exact mechanism is unclear, it is likely that heavy particle deposition in the airway evokes an intense inflammatory response that leads to subsequent airway fibrosis in much the same way as is believed to be true for nodular fibrotic diseases such as silicosis. These lesions may play an integral role in the pathophysiology of emphysema (Wright et al., 1992); however, the role of silica in the development of emphysema remains unclear.

Some investigators have questioned the relation between silicotic lesions and emphysema based on the lack of correlation between chest X-ray diagnosis of silicosis and emphysema in some epidemiology studies (Kinsella et al., 1990; Malmberg et al., 1993). Results of a recent report by Leigh et al. (1994), which examined the relation between quantified emphysema and measured (at autopsy) lung mineral content in 264 deceased coalworkers, do not support a relation between exposure to silica and the development of emphysema. The authors report that the lung content of silica may not have been high enough to show a true effect of silica. Silicotic nodules and mineral-dust-induced airway lesions that appear to be similar to those seen in humans were observed in rats in conjunction with emphysema following intratracheal exposure to quartz (Wright et al., 1988). A recent autopsy-based epidemiologic examination of nonsmoking South African gold miners by Hnizdo et al. (1994) determined that the degree of panacinar emphysema was related to the degree of fibrosis in hilar glands, a possible surrogate for silica exposure. Thus, the fact that some epidemiology studies have not observed a correlation between silicosis and emphysema may be due to low exposures and the difficulties with the diagnosis of silicosis from typical chest radiographs (Hnizdo et al., 1993; Amandus et al., 1992; Muir et al., 1989a,b; Bégin et al., 1988).

Becklake et al. (1987) observed a correlation between emphysema severity in gold miners who have silica and other exposures and the number of shifts worked in high dust areas. Hnizdo et al. (1991) subclassified the type of emphysema seen in these South African gold miners and concluded that both centrilobular and panlobular emphysema were related to cumulative dust exposure, and that centrilobular emphysema was associated with the presence of silicosis. The question of which dusts produce or contribute to the progression of these lesions, however, is an area that needs further study. It is known, for example, that cigarette smoke dramatically enhances the impact of mineral dust in inducing both small airway changes and emphysema. In fact, the Hnizdo et al. (1991, 1994) data suggest that, although silica exposure may cause emphysema in both smokers and nonsmokers, increased emphysema incidence is only statistically significant for smokers.

5.7.2 Airflow Abnormalities

Several recent studies have identified airway flow abnormalities in humans exposed to silica, among other dusts (Malmberg et al., 1993; Chia et al., 1992; Cowie and Mabena, 1991; Bégin et al., 1988). Bégin et al. (1988) observed the presence of silicotic nodules on computerized tomogram (CT) scans and chest X rays and found them to be associated with airflow limitation. Workers identified as having silicotic nodules from CT scans and X rays had abnormal maximum expiratory flow at 50% of the vital capacity and abnormal forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$), compared with dust-exposed controls for which nodules were not identified. This, plus the fact that FEV_1/FVC was unchanged between the two groups, indicates that small airway lesions were present. Laboratory animal experiments by Wright et al. (1988) and Churg et al. (1989) also correlated fibrotic lesions (of small airways) with measures of airflow obstruction in rats.

Some epidemiology studies (Malmberg et al., 1993; Chia et al., 1992; Cowie and Mabena, 1991) have reported a poor correlation between changes in lung function and chest radiographic changes indicative of silicosis. These findings do not rule out the presence of airway lesions but, more likely, are indicative of the problems associated with identification of silicotic lesions from chest X rays. As discussed in Section 5.4, Hnizdo and colleagues found that readings from chest radiographs were poor predictors of pathologic determinations of silicosis at autopsy (Hnizdo et al., 1993). Although anatomic lesions responsible for airflow changes have not been identified

fully, most of the human and animal evidence indicates that lesions of the small airway play an important role in pneumoconiosis (Wright et al., 1992). Newer diagnostic tools, such as high-resolution computed tomography (HRCT) are under development and should improve the understanding of the mechanisms and consequences of silica-induced lung injury (Begin et al., 1988). A recent investigation that found no relationship between pulmonary function tests and different chest X-ray classifications, did find that forced expiratory volume (FEV), maximal expiratory flow at 50% and 75% of FVC (MEF [50] and MEF [75]), and diffusion capacity all significantly decreased with increasing HRCT categories (Talini et al., 1995). Subjects with simple silicosis detected by HRCT had a lower FEV than subjects without silicosis.

5.8 EPIDEMIOLOGY STUDIES OF AMORPHOUS SILICA EXPOSURES

The various forms of inhalable, manufactured amorphous silica have been categorized as natural, fused, fumed, or precipitated (American Conference of Governmental Industrial Hygienists, 1991). Very little is known about health effects of fused silica in animals or humans. Even the noncrystalline (amorphous) structure of this glass is not well understood. The other forms of amorphous silica, which include pyrogenic or fumed silicas, have been found to be less toxic than crystalline silica in humans, animals, and cells (American Conference of Governmental Industrial Hygienists, 1991). Amorphous silica fume appears to be more toxic than precipitated silica.

Silica fume is the fume released during electrometallurgical processes in the manufacture of elemental silicon and silicon alloys, such as ferrosilicon. The disease process in workers exposed to silica fume originally was described as silicosis or acute silicosis (Princi et al., 1962). It is now recognized, however, that the X-ray pattern and symptom complex are different; the severity of the symptoms is less, and there is apparently no progression (American Conference of Governmental Industrial Hygienists, 1991). Repeated exposure to amorphous silica fume causes "ferro-alloy disease", which is characterized by recurrent fever over a period of 3 to 12 weeks with the appearance of X-ray markings similar to silicosis (Princi et al., 1962; Taylor and Davies, 1977). However, these lesions do not progress, and, in many cases, regress spontaneously.

Another form of amorphous silica, precipitated amorphous silica, is manufactured in several ways, including dehydrating sodium silicate, combustion of ethyl silicate, or by burning silicon

tetrachloride in air. These dusts have a large surface area (<40 to >400 m^2/g) (American Conference of Governmental Industrial Hygienists, 1991). They form layers around quartz particles, which may facilitate the toxic action of quartz. A study regarding exposure to precipitated amorphous silica examined medical records of 165 workers in two industrial facilities producing Hi-Sil™ and Silene™ in order to assess the clinical effects of exposure to fine particle precipitated amorphous silica (Wilson et al., 1981). The monthly exposure for each worker was graded on a scale of 1 to 4, and a cumulative exposure index was calculated for each worker by summing monthly dust exposure measured by personal airspace monitoring. A mean exposure index was calculated by dividing the cumulative exposure index by total months exposed. Linear regression analysis of the yearly change of pulmonary function parameters (FVC, FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$) showed no correlation with either the concentration (cumulative exposure index) or total years of exposure. Among 44 workers with a mean exposure of 18 years (range 10 to 35 years), the yearly declines of FVC and FEV_1 were similar to the overall group. Chest X rays of 143 workers taken prior to exposure to precipitated amorphous silica were compared with the most recent radiographs. Eleven of these workers (all with a previous history of working in a limestone mine or in a soda ash plant using limestone) had radiographic changes consisting of small rounded or irregular opacities. No worker with a history of exposure to only amorphous silica exhibited any radiographic evidence of lung lesions. Reported respiratory symptoms (cough and dyspnea) of the overall group correlated with smoking but not with exposure to amorphous silica.

None of the available reports on amorphous silica allow for the development of a concentration-response relationship and the establishment of a NOAEL. The development of silicosis observed by Taylor and Davies (1977) is likely the result of concurrent exposure to crystalline silica (American Conference of Governmental Industrial Hygienists, 1991). Exposure concentrations of silica fume that caused fume fever have not been measured, although they were described as massive.

5.9 CONTRAST BETWEEN SILICA AND OTHER PARTICLES

Workers with silica exposures have a much greater risk of contracting and dying of silicosis (and other pulmonary diseases) than do workers lacking such exposure. These observations have

been noted repeatedly by occupational medicine experts throughout the 20th century. However, occupational exposure to silica is not dissimilar to situations where workers are exposed to other hazardous particulate exposures, such as asbestos and cotton dust, because each produces a distinct pulmonary disease—asbestosis and byssinosis. Workers with predominately noncrystalline (i.e., amorphous) silica exposures such as diatomaceous earth miners or clay workers are not thought to have as great a risk of respiratory disease given equivalent dust exposure (Seaton, 1984). The role that respirable silica dust may play in the risk of chronic lung disease in a community from exposure to ambient particulate air pollution (PM_{10}) has not been assessed fully, although, from preliminary estimates discussed in Chapter 7, the silicotic effects of silica are not likely to contribute substantially to ambient chronic lung disease risk.

6. ANIMAL STUDIES OF NONCANCER EFFECTS FROM EXPOSURE TO SILICA

6.1 INTRODUCTION

Numerous investigators have demonstrated the pulmonary fibrogenic potential of silica in a variety of in vitro assays and in several animal species exposed by inhalation or intratracheal instillation. In vitro hemolysis and cytotoxicity assays have been used to characterize silica surface functionalities, which contribute to its bioactivity. The pathogenetic mechanisms of silica-induced lung injury are not understood fully; however, it is generally considered that both alveolar and interstitial macrophages play important roles (Bowden, 1987). Recent in vitro studies have focused on the ability of silica to activate alveolar macrophages and other lung cells to release oxidants, cytokines, and growth factors, which are believed to play a role in inflammation processes that lead to silicosis. Findings from these in vitro studies support the concept that silica-induced secretion of inflammatory proteins, such as tumor necrosis factor α, are key to the pathogenesis of silicosis. However, the continuous recruitment of fibroblasts, polymorphonuclear leukocytes (PMNs) or neutrophils, lymphocytes, and plasma cells to alveolar and interstitial sites and the multifocal distribution of lesions suggest that the development of silica-related pulmonary lesions is a complex process. It is beyond the scope of this document to provide a complete review of the findings of in vitro studies. The reader is referred to other recent reviews of this topic for further details (Driscoll, 1995; Saffiotti et al., 1993).

The fibrotic effects of silica may vary depending on species, as well as on the physical form of silica employed. For example, hamsters exhibit a weaker fibrogenic response than do other rodents, dogs, or humans (Uber and McReynolds, 1982), and mice intratracheally injected with silica had a milder fibrogenic response than rats (Hatch et al., 1984). The degree of fibrosis in rats intratracheally injected with different forms of silica was least with amorphous (fused) silica, increased with quartz, and was highest with tridymite, despite similar silica content, size distribution, and solubilities for all forms (King et al., 1953; Englebrecht et al., 1958).

Although renal effects resulting from silica exposure have been observed in humans (see Chapter 5, Section 5.2.5), no data were located documenting similar effects in experimental animals by the inhalation or intratracheal routes of exposure. Osorio et al. (1987) noted that silica gel (SiO_2 suspension in physiological fluid) administered by intraperitoneal injection or abdominal incision had been reported to induce a variety of renal lesions in rats and rabbits.

Commonly used parameters to follow the pulmonary effects of silica exposure of experimental animals are lung weight, development of fibrous tissue and collagen, cytotoxicity, biochemical indices, and immunologic responses. In most of the available studies, endpoints other than pulmonary toxicity were not examined routinely. Few studies provided more than modest exposure-response data from which NOAELs or lowest-observed-adverse effect levels (LOAELs) could be derived, thus necessitating comparisons among studies in which experimental conditions may vary considerably.

Table 6-1 summarizes the key subchronic and chronic exposure studies that documented a concentration-response relationship in laboratory animals. A more complete review of available subchronic and chronic inhalation studies is provided in the sections that follow.

6.2 FINDINGS FROM SUBCHRONIC STUDIES

6.2.1 Crystalline Silica Subchronic Studies

Burns et al. (1980) related early immunological changes with eventual cytological changes in the lungs by exposing female Balb/c mice, maintained in exposure chambers, to crystalline silica (Min-U-Sil™; MMAD = 2.0 μm; geometric standard deviation [σ_g] not given) at a concentration of 4,932.4 ± 235.4 $\mu g/m^3$ for 6 h/day, 5 days/week for 3, 9, 15, 27, 33, or 39 weeks. Control mice were kept in identical chambers and breathed only filtered air. Groups of six mice were removed at Weeks 3, 9, 15, 21, and 27 and were challenged with Escherichia coli antigen given as an aerosol. Silica exposure greatly reduced the ability of splenic lymphocytes to respond to the antigen in the spleen at all times tested; in the mediastinal lymph nodes, there was an initial increase in the number of anti-E. coli plaque-forming cells at 9 weeks, followed by a decrease of this response at all subsequent time periods. At Weeks 15, 21, and 27, the spleen/body weight ratio of exposed animals was significantly higher than those of controls. Lung tissue of animals

TABLE 6-1. HUMAN EQUIVALENT CONCENTRATIONS (HECs) AND EFFECTS FOR NO-OBSERVED-ADVERSE-EFFECT LEVELS (NOAELs) AND LOWEST-OBSERVED-ADVERSE-EFFECT LEVELS (LOAELs) REPORTED IN SUBCHRONIC (≥3 MONTHS) AND CHRONIC CRYSTALLINE SILICA INHALATION STUDIES

Species	Exposure Duration	NOAEL (mg/m^3)[a]	LOAEL (mg/m^3)	$LOAEL_{HEC}$[b] (mg/m^3)	Critical Effect	Reference
Rat	6 h/day, 5 days/week for 24 mo	NR	1.0	0.18	Subpleural and peribronchial fibrosis, focal lipoproteinosis, cholesterol clefts, enlarged lymph nodes, and granulomatous lesions in the walls of large bronchi; doubling of lung collagen content.	Muhle et al. (1989)
Mice	8 h/day, 5 days/week for 150, 300, or 570 days	NR	2.0	0.36	Suppressed response to aerosol of Escherichia coli (i.e., formation of plaque-forming cells in spleen) at 150, 300, and 570 days; reduced ability of alveolar macrophages to phagocytize Staphylococcus aureus at 570 days; reduced T-lymphocyte-mediated cytolysis of allogeneic tumor cells at 185 days.	Scheuchenzuber et al. (1985)
Mice	6 h/day, 5 days/week for 3, 9, 15, 27, 33, or 39 weeks	NR	5.0	0.9	Suppressed response to aerosol of E. coli (i.e., formation of plaque-forming cells in spleen) at 15, 27, 33, and 39 weeks; increased spleen/body ratios at 15, 21, and 27 weeks; induced pulmonary fibrosis (fibrotic nodules of collagen, fibroblasts, lymphocytes, and silica-filled macrophages) at 39 weeks.	Burns et al. (1980)
Rat	6 h/day, 5 days/week for 6 mo	NR	2.0	0.36	Increased collagen and elastin content of lungs; caused birrefringent crystals in foamy cytoplasm of macrophages that had accumulated in end-airway luminal spaces; induced Type II cell hyperplasia in alveolar compartment and intralymphatic microgranulomas around bronchioles in some animals.	Kutzman et al. (1984a)
Rat	6 h/day, 5 days/week for 6 mo; plus 6-mo incubation period	NR	2.0	0.36	Increased weight and collagen, elastin, deoxyribonucleic acid, and protein content of lungs (particularly at higher exposures of 10 and 20 mg/m^3), indicating continued tissue proliferation and fibrogenesis during incubation; increased number of silica particles and inflammation at end-airways, focal fibrosis and intralymphatic granulomata, and overall severity and frequency of lesions.	Kutzman et al. (1984b)
Dog	6 h/day, 5 days/week for up to 2.5 years	NR	0.2	[c]	Cellular infiltration of particles in lungs and hyalinized fibrotic nodules in lymph nodes. Increased infiltration of macrophages into perivascular and peribronchial areas of lungs.	Wagner et al. (1968)

[a]NR = Not reported.
[b]Human equivalent concentration (HEC) calculated using methods described in U.S. Environmental Protection Agency (1994a).
[c]HEC could not be calculated due to lack of lung parameter data for dogs.

exposed to silica from Weeks 3 to 21 exhibited varying degrees of lymphoid infiltration in the absence of other significant changes. Beginning at Week 24 and subsequent exposure intervals, aggregates of silica-filled macrophages were observed histologically. Aggregates of macrophages were not detected in most control animals. By Week 39, fibrotic nodules composed of collagen, fibroblasts, lymphocytes, and silica-filled macrophages were found. The nodules were located at the periphery of the lung near the pleural surfaces.

Fischer 344 rats (24/sex), approximately 10 weeks old and weighing 190 to 260 g, were exposed 6 h/day, 5 days/week to crystalline silica (Min-U-Sil™) at an average dust concentration of 10 mg/m^3 for periods of 2, 4, 6, or 12 mo (Vuorio et al., 1989). The silica employed, Min-U-Sil™, had an MMAD of 1.87 ± 1.26 μm. Control animals were exposed to air in identical chambers. Development of fibrosis was followed by measurement of lung weight (as wet weight), histological examination, and determination of lung collagen content (as hydroxyproline). During the 12-mo experimental period, there was a steady increase in lung weights to a level approximately 2 to 2.5 times higher than those of controls; however, the animal body weights remained constant during the same time period. Histological examination revealed a progressive pulmonary inflammation and fibrosis in the silica-exposed group. There was an increase in pulmonary collagen content (as evidenced by increased hydroxyproline) together with changes in cellularity and the metabolic activity of the lungs, as determined by pulmonary procollagen messenger ribonucleic acid (mRNA) content. Silica-exposed animals showed a time-dependent increase in procollagen mRNA that was greater at each time point when compared statistically with controls. The highest levels of procollagen mRNA were seen in young animals, suggesting that during pulmonary development, collagen metabolism in lungs is even greater than during the development of fibrosis.

Kutzman (1983, 1984a,b) evaluated the relationship between functional tests and compositional and structural alterations in the rat lung induced by subchronic exposure to silica dust (Min-U-Sil™ 5; MMAD = 2.4 μm; σ_g = 2.0). Fischer-344 (F344) rats were exposed for 6 h/day, 5 days/week for 3 or 6 mo to 0, 2, 10, or 20 mg silica/m^3. A separate group of rats was retained 6 mo after the 6-mo exposure to ascertain reversal or progression of the lesions. A series of respiratory physiology tests was performed on animals of each group. The 3-mo exposure to silica did not change responsiveness of animals to carbon dioxide-induced hyperventilation, nor did silica have a concentration-dependent effect on partial pressure of arterial blood gases or

blood pH. None of the parameters of normal tidal breathing were affected by exposure. Lung volumes of exposed rats were not different from controls, although there were overall silica effects for total lung capacity and functional residual capacity. The quasi-static compliance and the diffusing capacity for carbon monoxide were not altered, although the 20-mg/m^3 group exhibited a downward trend. The distribution of ventilation exhibited an overall silica effect, suggesting airflow bifurcation. However, the flow volume dynamics and the upstream airway resistance of F344 rats were unaffected by the silica concentrations tested. Frontal chest X rays were taken of rats from each exposure group prior to necropsy. No evidence of silica-induced lung disease was observed from the X rays of exposed rats (Kutzman, 1984a,b). The X rays from exposed rats were all indistinguishable from those of control animals; yet, subsequent analysis of rats at necropsy revealed concentration-related changes in lung composition and lung physiology, a finding similar to that which is observed in humans (Hnizdo et al., 1993). Amounts of protein, deoxyribonucleic acid (DNA), elastin, collagen, and water content of lungs were assessed. Overall silica-dependent increases in collagen and elastin were reported, 110, 111, and 116% for collagen (as hydroxyproline) and 102, 109, and 109% for elastin, respectively, for each of the exposure groups relative to control. Protein, DNA, and water content did not change. Histopathologically, birrefringent crystals were evident in the foamy cytoplasm of macrophages that had accumulated within end-airway luminal spaces. In some animals, Type II cell hyperplasia was evident in the alveolar compartment. Intralymphatic microgranulomas surrounding the bronchioles also were evident, particularly in the 20-mg/m^3 group, less frequently in the 10 mg/m^3 group, and in only 1 of 24 animals exposed to 2 mg/m^3.

Rats exposed similarly for 6 mo showed overall greater silica-dependent effects with the 20-mg/m^3 group being clearly affected as indicated by the significance of multiple comparison tests. The 2- and 10-mg/m^3 groups showed some effect depending on the functional variable, but these effects reflected only marginally in statistical testing. For example, distribution of ventilation showed obstructive impairment (small airway effects), as indicated by moment analysis (0, 10, and 33%, respectively, with only the 20-mg/m^3 group reaching significance); analogous effects were found with lung displacement volume and indices of trapped gas within the lung. Most static and dynamic parameters of function were affected only slightly or not affected by the silica exposure, although the overall trend suggested incipient restrictive lung disease (i.e., a stiffer lung, in the 20-mg/m^3 group). The animals at 20 mg/m^3 had reduced partial oxygen pressure

(pO_2) levels and could not hyperventilate to carbon dioxide (CO_2) to the same extent as could control animals. No evidence of small airway disease was apparent functionally, but this disease was likely the result of hyperplasia and connective tissue proliferation at the end-airway, which affected more the expansive diameter of the airway, rather than enhancement of the airway's collapsibility or reduction of lumen size. Amounts of protein, DNA, elastin, collagen, and water content of lungs were assessed. Significant concentration-dependent increases were observed in both collagen and elastin levels. The amount of collagen relative to controls was 116, 128, and 136% in the 2-, 10-, and 20-mg silica/m^3 exposure groups, respectively. Total elastin in the 2-, 10-, and 20-mg silica/m^3 exposure groups was 107, 119, and 130%, respectively, of the amount in the lungs of control animals. Protein, DNA, and water content were not altered significantly in exposed groups.

Microscopic examination at necropsy revealed concentration-related signs of respiratory silicosis in exposed animals. Inflammatory reactions near end-airways were observed in all exposure groups, with the worst reactions and higher frequency in the rats exposed to 20 mg/m^3. Type II cell hyperplasia and, in some cases, focal fibrosis resembling silicotic nodules, were observed. Other studies (Miller et al., 1986; Saffiotti et al., 1994) have shown that in silica-treated rats, the Type II cells are morphologically and functionally different from those seen in normal lungs. The Type II cells are generally large, have an increased amount of enzymes related to phospholipid synthesis and cell proliferation (Saffiotti et al., 1944), and have a higher concentration of mRNA related to surfactant apoprotein synthesis (Miller et al., 1986). Intralymphatic microgranulomas were common. Similar, but less severe lesions were observed in rats exposed to 10 mg silica/m^3. In the lowest exposure group, the pathologic effects were limited to inflammation and intralymphatic microgranulomas in the lungs of 3 of 24 rats. Lungs from control groups contained no specific alterations.

In the companion study where animals were exposed to 0, 2, 10, and 20 mg/m^3 of SiO_2 for 6 mo and returned to clean air for 6 mo before assessment, the silica lesions appeared to have worsened. Virtually all functional parameters were significantly affected by silica, most notably in the 20-mg/m^3 group. These effects (particularly in the 20-mg/m^3 group) were consistent with restrictive disease, such as decreases in static compliance and in diffusion capacity for carbon monoxide. The flow volume curve also suggested stiffer lungs but indices of ventilation distribution were depressed relative to controls indicating that there was a small airway

component (probably peribronchial fibrosis or interstitial fluid accumulation). Collagen was elevated to 111, 120, and 176% and elastin 108, 109, and 140% of controls for the respective exposures. Protein and DNA increased 6, 7, and 55% and 8, 11, and 55%, respectively, indicating continued tissue proliferation and fibrogenesis. The presence of many foamy macrophages and eosinophilic material in the alveolar spaces suggested lipoproteinosis. Histologically, silica particles and ongoing inflammation at the end-airways were readily apparent in a concentration-dependent manner. Focal fibrosis and intralymphatic granulomata also were present. Overall, the severity and frequency of lesions within the lung were indicative of maturation and progression of the fibrotic disease. Both incidence of lesions and degree of severity were worse with this treatment than at the 6-mo time point without the recovery period. The disease was clearly progressive at all concentration levels. Stepwise discriminant analysis was used to identify those raw and normalized pulmonary-function and lung-composition variables that best distinguish among the four exposure groups. The variables found to have the greatest power for discriminating among the exposure groups were total lung weight, total collagen, and the amount of elastin and protein per unit dry weight. Significant alterations in these parameters at the lowest exposure level tested and microscopic analysis revealing silicotic lesions at the higher exposure levels indicate that 2 mg silica/m^3 represents a LOAEL for this study. None of the functional variables had significant discriminating power to distinguish the exposure groups.

Groups of male syngeneic PVG rats bred under specific pathogen-free conditions (age 15 weeks) were exposed to pure quartz dust (Sikron F600; A9950 Euro Standard) for 7 h/day, 5 days/week in exposure chambers at target concentrations of 10 or 50 mg/m^3 of respirable dust (MMAD not reported) (Vincent and Donaldson, 1990; Donaldson et al., 1990). The animals were removed at time points between 2 and 75 days of exposure for bronchoalveolar lavage (BAL) to assess leukocyte response. Quartz exposure produced a time-dependent increase in the number of leukocytes, much earlier in onset and greater in magnitude at 50 mg/m^3 than at 10 mg/m^3. There also were significantly increased lactate dehydrogenase (LDH) and N-acetyl-ß-D-glucosaminidase activities at both 10 and 50 mg/m^3 over the 75-day exposure period. In a second experiment, groups of rats were exposed similarly to airborne quartz dusts for 32 or 75 days, removed from exposure chambers, and allowed to recover for 64 days. There was a marked increase in pulmonary inflammation that continued after cessation of exposure to quartz.

Benson et al. (1986) exposed F344 rats (72/sex) in whole body chambers to 38 mg/m^3 α-quartz (Min-U-Sil™), 7 h/day for 4 weeks. The quartz MMAD was 2.2 μm, with a σ_g of 1.8. A corresponding group of control animals (72/sex) was exposed to filtered air. Animals were sacrificed at 2, 4, and 6 weeks after initiation of exposure and functional, biochemical, and cytological tests were performed. There were no changes in respiratory function after 4 weeks of exposure. An inflammatory response in the lungs, as indicated by an influx of PMNs in the bronchoalveolar regions, was observed after 2 and 4 weeks. Only minimal biochemical changes in the lungs were observed after 2 weeks, but, after 4 weeks of quartz exposure, there was a fivefold increase in airway LDH activity (indicating cell damage), a fivefold increase in airway protein content (indicating increased permeability of the alveolar/capillary barrier), and a sevenfold increase in airway β-glucuronidase activity (indicating release of lysosomal enzymes in the lung). The number of lymphoid cells in the pulmonary lymph nodes was increased significantly (p value not reported) in quartz-exposed animals and remained elevated for at least 2 weeks after cessation of exposure.

Bice et al. (1987) also evaluated the pulmonary immunotoxicity of inhaled quartz. Fischer-344 rats were exposed to 38 mg/m^3 α-quartz (Min-U-Sil™; MMAD = 2.2 μm, σ_g = 1.8), 7 h/day for 4 weeks. A corresponding group of control animals was exposed to filtered air. Groups (5/sex) of exposed and control rats were immunized by intratracheal instillation of sheep red blood cells (10^8 cells) at Weeks, 6, 40, or 52 from the initiation of the exposures. Cellularity of lung-associated lymph nodes and antibody-mediated immunity were evaluated 7 days after immunization. Lung and lymph node tissues were examined histologically. The lung burden at the end of the 20-day exposure was 3.7 ± 2.8 mg quartz/g lung. Inhalation of quartz increased the number of lymphoid cells at each of the sacrifice times, caused suppression of antibody responses at 52 weeks after start of exposure, and produced cellular changes in lungs and lung-associated lymph nodes. Using a rat silicosis model, investigators have demonstrated an increase in the number of lymphocytes in lavage fluid, with a predominance of helper T-lymphocytes (Struhar et al., 1989).

In a protocol designed by Bennett et al. (1988) to provide a rapid assessment of the fibrogenic potential of inhaled materials, groups of young Alpk:AP rats were exposed nose-only to a respirable aerosol of α-quartz (Min-U-Sil™; MMAD = 1.4 μm, σ_g not reported), 6 h/day, 7 days/week for 28 days. The study used rats of both sexes and two different ages (8 and

13 weeks) at first exposure. The cumulative exposure concentrations, calculated by multiplying the daily mean concentrations by the duration of exposure, were given as 8,486 and 6,314 mg/m^{-3}·h (units as reported by investigators) for the younger and older rats, respectively. Control animals were exposed to air. After exposure, the rats were observed for up to 1 year, followed by histopathological examination of the lungs. Interim necropsies (4 animals/sex after 4, 17, and 34 weeks of exposure) were conducted to estimate the rate and severity of fibrogenic lesions. Lung weights of silica-exposed rats were increased slightly (20%) immediately after exposure and continued to increase at each time point; at the end of the 1-year holding period, their lungs were up to six times heavier than those of controls. Multiple foci of foamy alveolar macrophages, associated with PMN infiltration, were observed at the end of the 28-day exposure period. The fibrotic lesions were characterized by granulomatous inflammation in the major bronchioles, progressing to perivascular and pleural granulomata and multifocal alveolar lipoproteinosis during the holding period. A progressive granulomatous inflammation accompanied by various degrees of fibrosis was the principal effect seen in the tracheobronchial and mediastinal lymph nodes. The type of lesions observed in rats from both age and sex groups was similar throughout the study, although the lesions were more severe in the older (at first exposure) rats than in the younger ones, especially at later time points.

Table 6-1 provides a summary of subchronic (>3 mo) and chronic studies that exposed laboratory animals to less than 10 mg/m^3 crystalline silica.

6.2.2 Amorphous Silica Subchronic Studies

Warheit et al. (1991a) exposed CD rats by inhalation (nose-only) to Ludox™ (a colloidal suspension of amorphous silica) at concentrations of 0, 10, 50, or 150 mg/m^3, 6 h/day, 5 days/week. The MMADs for the three Ludox exposures were 3.7, 3.3, and 2.9 μm, respectively (σ_g not reported). Groups of six rats from each of the exposure concentrations were evaluated after 2 and 4 weeks of exposure and at 3 mo after a 4-week exposure to Ludox™. Lung fluids and cells were lavaged, and cellular and biochemical parameters were determined. Exposure to 150 mg/m^3 for 2 or 4 weeks or to 50 mg/m^3 for 4 weeks produced pulmonary inflammation as evidenced by increased numbers of PMNs, protein content, and LDH and alkaline phosphatase (AP) activities in BAL. In vitro phagocytic and chemotactic responses of exposed alveolar macrophages were functionally impaired . Most biochemical parameters returned to

normal after a 3-mo recovery period. Autoradiographic studies showed that the labeling index of terminal bronchiolar and lung parenchymal cells was increased in the mid- and high-concentration groups after 2 and 4 weeks of exposure and returned to normal following recovery. No changes in biochemical or cellular kinetic indices were noted at 10 mg/m^3, a concentration that can be considered a NOAEL.

Kelly and Lee (1990) exposed rats (25/group, strain not given) nose-only to Ludox™ at concentrations of 0, 10, 50, or 150 mg/m^3, 6 h/day, 5 days/week for 4 weeks (particle size distribution not given). Five rats were necropsied at the end of the exposure period, and 10 each at 10 days and 3 mo postexposure. No pulmonary effects were seen at the lowest concentration. At 50 and 150 mg/m^3, there was a concentration-related pulmonary response in the alveolar duct region characterized by silica-dust-laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia. Tracheal and mediastinal lymph nodes were enlarged due to the silica-dust-laden alveolar macrophages and tissue hyperplasia. The pulmonary lesions decreased progressively during the 3-mo postexposure observation period. The NOAEL for this study was also 10 mg/m^3.

6.3 FINDINGS FROM CHRONIC STUDIES

6.3.1 Crystalline Silica Chronic Studies

Muhle et al. (1989) exposed F344 rats (50/sex) to 1 mg/m^3 quartz (DQ-12) in whole-body chambers, 6 h/day, 5 days/week for 24 mo using a dry aerosol technique. The quartz MMAD was 1.3 μm (σ_g = 1.8). Parallel groups were exposed to filtered air only. No treatment-related effects on life span or causes of death were observed; the median life span was 750 days from initiation of exposure. By the end of the 24-mo exposure period, the principal nonneoplastic finding in the silica-exposed animals was extensive subpleural and peribronchiolar fibrosis described as unlike the nodular fibrosis seen in human silicosis. The lung collagen content more than doubled in the silica-exposed group. Also seen were focal lipoproteinosis, cholesterol clefts, enlargement of lymph nodes, and a granulomatous response in walls of some of the larger bronchi. Lung tumors were first observed after 21 mo of exposure.

Immunologic responses were determined in groups of female Balb/c mice following inhalation of crystalline silica (Min-U-Sil™), 8 h/day, 5 days/week for 150, 300, or 570 days (Scheuchenzuber et al., 1985). The dust concentrations in inhalation chambers were adjusted to approximately 2 mg/m^3 of respirable silica dust, with particle sizes of 2.1 μm or smaller. Mice exposed to dusts for all time periods were immunized with E. coli antigen for determination of specific humoral responses, whereas other groups of mice exposed for 570 days were used for additional immunoassays. Silica inhalation suppressed the number of specific plaque-forming cells in the spleen in response to E. coli and, when tested after 570 days of exposure, reduced the ability of alveolar macrophages to phagocytize S. aureus in vitro. Proliferation of splenic lymphocytes after stimulation with allogeneic lymphocytes from C57/BL mice also was unaltered, but the ability of these cells to kill tumor cells from the same strain of mice was reduced severely. The authors indicated that the effects of prolonged exposure were confounded by age-related immunologic changes. Most of the immunologic responses occurred after relatively short exposures, increased to some extent with exposure, and were persistent.

Rats, dogs, and guinea pigs were exposed by inhalation to 0.2 μg/m^3 (79 rats, 16 dogs, 57 guinea pigs) and 0.5 mg/m^3 (82 rats, 17 dogs, 69 guinea pigs) (2 and 5 mppcf, respectively) of flux-calcined diatomaceous earth containing 61% cristobalite, 6 h/day, 5 days/week for up to 2.5 years (Wagner et al., 1968). Another set of rats and guinea pigs (46 and 20, respectively) was exposed to 5 mg/m^3 (50 mppcf) 1 h/day, 3 days/week (a cumulative weekly exposure of 150 mg/m^3 × hours). Still another set of rats and guinea pigs (53 and 20, respectively) received both the 0.5 and 5 mg/m^3 exposure regimens described above. The MMAD for the dust used was 0.7 μm (σ_g = 2.1). Few histopathological changes were found in the lungs of any of the three species for any of the exposure regimens; no changes were seen in 10 additional tissues (heart, liver, kidney, spleen, adrenal gland, duodenum, hepatic lymph nodes, trachea, pancreas, and urinary bladder) examined histologically. There was, however, an increase of infiltration of macrophages into perivascular and peribronchial areas of the lungs in all three species at all exposure levels, with rats and guinea pigs exhibiting similar responses. The responses at 0.2 and 0.5 mg/m^3 showed a good correlation with exposure concentration and duration. Although frank pulmonary fibrosis did not develop in rats, dogs, or guinea pigs, cellular infiltration in the lung and hyalinized fibrotic nodules in the lymph nodes developed in dogs at 0.5 mg/m^3, with scattered nodules observed at 0.2 mg/m^3. Perhaps the most important finding of this study was that the

severity of the response in rats was only slightly higher, and there was no perceptible difference in the reaction of guinea pigs to three peak (1-h) exposures to 50 mg/m^3 versus five daily (6-h) exposures to 5 mg/m^3. Thus, similar effects were observed, given the same overall weekly, cumulative exposure, regardless of the continuous-versus-peak nature of the exposures.

Holland et al. (1986) exposed 62 female F344 rats, nose-only, to quartz (Min-U-Sil™) dust at a concentration of 12 mg/m^3, 6 h/day, 4 days/week for 83 weeks. The MMAD of quartz particles was 2.24 ± 0.2 μm (σ_g = 1.75). Control groups consisted of 62 rats exposed to the same inhalation protocol using filtered air only (sham controls) and 15 rats housed in the same location but not manipulated. Most exposed animals (54/60) surviving beyond 400 days exhibited pronounced pulmonary fibrosis, characterized by granulomas and deposition of collagenous connective tissue. Silicotic nodules and pleural plaques were seen in most quartz-exposed animals. Emphysema often accompanied the fibrotic changes, with alveolar proteinosis in animals with advanced fibrosis. In controls, fibrosis was seen in only one animal. The mean lifespan of the quartz-treated group was within 10% of that of the sham control group.

Dagle et al. (1986) exposed F344 rats (144/sex) to 50 mg/m^3 quartz (Min-U-Sil™ 5), 6 h/day, 5 days/week for up to 24 mo. Respirable dust concentrations (TWA) were 51.6 mg/m^3 with a range of MMADs of 1.7 to 2.5 μm (σ_g = 1.9 to 2.1). Controls were exposed to air only. Subgroups of five rats were killed at 4-mo intervals to study the development of lung lesions. The mean survival time of rats exposed to quartz for 24 mo was decreased (539 days compared with 688 days for the control group). The survival curves of the serially withdrawn rats suggested a cumulative concentration-response relationship. The mean survival times following initial exposure were 653, 585, 556, or 554 days for the subgroups (n = 5) withdrawn from quartz exposure at 4, 8, 12, or 18 mo, respectively. Quartz-exposed rats had lower body weights (consistently observed only after at least 12 mo of exposure) and increased lung weights (as wet weight) and volumes. Pathologic changes at 4 mo included grossly enlarged lungs with diffuse mottling, brown-to-purple discoloration, and grey-to-white subpleural foci. These changes generally became more severe with time. Histopathologically, an increased number of alveolar macrophages, alveolar proteinosis, alveolar epithelial metaplasia, pulmonary adenomatosis, interstitial lesions, and lymphoreticular hyperplasia were observed. Occasional nodules of fibrosis were seen in rats surviving longer than 12 mo. None of 47 female and 42 male controls experienced either nodules or tumor formation.

6.3.2 Amorphous Silica Chronic Studies

Groth et al. (1981) compared the pulmonary toxicity of inhaled synthetic amorphous fused silica (silica F), precipitated silica (silica P), and silica gel (silica G) in rats, guinea pigs, and monkeys. Eighty male Sprague-Dawley rats (300 to 380 g), 20 male Hartley guinea pigs (400 to 800 g), and 10 adult male cynomolgus monkeys (2,300 to 5,400 g) were exposed to silica dusts at a concentration of 15 mg/m^3 (7 to 10 mg/m^3 respirable dust), 5.5 to 6 h/day, 5 days/week, for up to 18 mo. An equal number of animals served as controls. The particle sizes (geometric mean) were 0.17, 0.27, and 0.38 μm for silica F, G, and P, respectively. Rats were sacrificed serially after 3, 6, and 12 mo of exposure, and guinea pigs and monkeys after 10 to 18 mo of exposure. All the animals were sacrificed at the end of the respective exposure periods. The most significant effect of exposure to all three amorphous silicas occurred in monkeys and was confined to the lungs and lymph nodes, which contained large numbers of macrophages and mononuclear cell aggregates, sometimes significantly reducing the size of the bronchiolar lumen. Although reticulin fibers were found in aggregates in all three silica groups, collagen and early nodular fibrosis was present only in monkeys exposed to silica F. Few silica-containing macrophages were seen in the lungs and lymph nodes of rats and guinea pigs exposed to any of the silicas.

Eleven tests of pulmonary function were conducted to assess the degree of respiratory impairment in monkeys exposed to silica F, P, or G for 14 mo (Groth et al., 1981). Functions that were decreased at the end of the study period included the lung volume measurements of FVC, inspiratory capacity, and TLC following exposure to silica F and P. Resistance, compliance, forced expiratory flow at the last 10% expired ($FEF_{10\%}$), and closing volume (all measurements of lung ventilatory mechanisms) were decreased in monkeys exposed to silica F and G. The greatest alterations were in compliance, $FEF_{10\%}$, and residual volume/TLC. The authors noted that, overall, respiratory impairment appeared to be most pronounced in silica F-exposed monkeys. Except for increased AP activity in silica F-exposed monkeys, there were no statistically significant differences between silica-exposed and control groups with regard to clinical chemistry and hematology parameters. The effect on AP did not correlate with any observed pathology and was not attributed to silica exposure. Under the conditions of this experiment, silica F appeared to cause more severe pulmonary effects than did either silica P or G. Possible contributing factors listed were smaller silica F particle size and greater aluminum and iron content of silica P and G. Aluminum and iron compounds have been reported to reduce the fibrogenic potency of silica,

providing variable protection (Heppleston, 1984). Studies of sheep have shown that aluminum salts, but not aluminum oxide, can prevent the development of silicosis and promote silica clearance from the lung (Dufresne et al., 1994; Dubois et al., 1988).

Schepers (1981) exposed albino Wistar-strain Sprague-Dawley rats to a precipitated amorphous silica (Hi-Sil™ 233) at an average dust concentration of 3.57 mg/ft^3 (126 mg/m^3), 8 h each day of the week for 15 mo; rabbits and guinea pigs were exposed to the same concentration for 12 and 24 mo, respectively. Altogether, 496 animals were used in the study; 270 were exposed to silica, and 226 served as controls. The silica particles with a median size of 2 to 5 μm (with ≈80% < 5 μm) exhibited significant clustering. There was no significant difference in mortality between exposed and control animals. Lung weights (as dry weight) increased with silica exposure but returned to normal after a 9-mo postexposure period. The primary effects in the three species were limited to macrophage accumulation in alveoli, bronchioles, and lymphoid tissues and mild proliferation of reticulin fibers in interstitial tissues. Macrophage accumulation was considered mild in rats but was more evident in rabbits and guinea pigs. Guinea pigs exhibited greater macrophage infiltration of lymphoid tissue compared with that seen in the alveoli. In rabbits, the macrophage accumulation tended to be perivascular and was peribronchial in guinea pigs. Almost complete reversal of all responses occurred when dust exposures were discontinued for 12 mo. Bronchial and tracheal epithelial cells remained intact, and no pleural changes or neoplastic effects were noted after the 12-mo postexposure period.

6.4 CONTRASTS BETWEEN AMORPHOUS AND CRYSTALLINE SILICA

A few studies have been carried out to compare the effects of inhaled crystalline and amorphous silica particles. Reuzel et al. (1991) compared the pulmonary toxicity of three amorphous silicas with that of quartz dust in a subchronic inhalation study with specific pathogen-free-bred Wistar rats. Groups of 70 male and 70 female rats (age 6 weeks) were exposed to 0, 1, 6, or 30 mg/m^3 Aerosil™ 200, 30 mg/m^3 Aerosil™ R 974, 30 mg/m^3 Sipernat™ 22S, or 60 mg/m^3 quartz, 6 h/day, 5 days/week for 13 weeks. The animals were sacrificed serially at the end of the exposure period and 13, 26, 39, and 52 weeks postexposure. Because the very small particles of the amorphous silicas formed agglomerates and aggregates, the MMADs could not be

determined; the range of the geometric particle size distribution was 1 to 120 μm. Quartz particle sizes varied between 0.1 and 25 μm. Aerosil™ 200, a hydrophilic silica, was selected as the primary test material because it is a widely used grade with a propensity to generate airborne particles. Aerosil™ R 974 was chosen because it is produced by chemical treatment of Aerosil™ 200, transforming it into a hydrophobic form; and Sipernat™ 22S, a hydrophilic material, was chosen because it has the same specific surface area as Aerosil™ 200.

Although body weight gains of quartz-exposed rats were not affected during the treatment period, a progressive reduction in weight gain was seen throughout the postexposure period. A slight (5 to 10%) decrease in body-weight gain occurred in males exposed to 30 mg/m^3 Aerosil™ 200 or Sipernat™ 22S at the end of exposure, but body weights returned to normal 52 weeks following cessation of exposure. Serial histological examinations revealed that PMN counts were increased in most exposure groups but returned to normal within 13 weeks postexposure; in quartz-exposed animals, the PMN counts remained high during the entire postexposure period.

All four chemicals induced increases in lung weight (at all concentrations tested) and pulmonary lesions, such as accumulation of alveolar macrophages, inflammation, alveolar bronchiolization, and fibrosis. Most of the rats exposed to the amorphous silicas or quartz had swollen and spotted lungs with spongy consistency and large lung-associated lymph nodes at the end of exposure. These gross changes disappeared at 26 weeks postexposure in all rats treated with the amorphous silicas, but persisted during the whole observation period in rats treated with quartz. Histopathological examination of the lungs revealed mild pulmonary effects (accumulation of alveolar macrophages, intraalveolar polymorphonuclear leukocytic infiltration, and increased septal cellularity) in rats exposed to 1 mg/m^3 Aerosil™ 200, the lowest concentration tested. Alveolar bronchiolization was observed mainly in males exposed to 6 or 30 mg/m^3 Aerosil™ 200 or to Aerosil™ R 974. Focal interstitial fibrosis was seen first in some animals 13 weeks postexposure to 30 mg/m^3 of quartz and each of the amorphous silicas. This lesion disappeared during the subsequent observation period in rats exposed to Aerosil™ R 974 or Sipernat™ 22S but became more severe in rats exposed to Aerosil™ 200 or quartz. In addition, rats exposed to 30 mg/m^3 Aerosil™ 200, Aerosil™ R 974, or quartz developed granulomatous lesions. Silicosis (defined by the authors as formation of collagen fibers and hyalinization of the granulomatous lesions) was observed only in quartz-exposed rats. The effects

on the respiratory tract induced by the amorphous silicas were most pronounced at the end of the exposure period, but generally disappeared within 1 year postexposure. Of the amorphous silicas examined, Aerosil™ 200 induced the most severe changes in the lungs, with only partial recovery, and Sipernat™ 22S induced the least severe, completely reversible changes. The quartz-induced pulmonary changes were comparable to those induced by Aerosil™ 200 at the end of the exposure period, but progressed thereafter, reaching a plateau at about 6 mo postexposure. The animals did not recover during the subsequent 6 mo. Additional treatment-related effects, focal necrosis of the nose and rhinitis, occurred mainly in animals exposed to the amorphous silicas and only at the end of the exposure period; a slight degeneration of the nasal epithelium was seen in all treated groups. The nasal effects were reversible and were considered nonspecific irritating effects of the amorphous silicas.

Data by Pratt (1983) present evidence that the pathogenicity of the crystalline forms of silica differs from that of the amorphous forms. Guinea pigs were exposed by inhalation to cristobalite (45% crystallized; the remainder diatomaceous earth) or amorphous silica (diatomaceous earth) at average dust concentrations of 150 mg/m^3 or 100 mg/m^3, respectively, 7 to 8 h/day, 5.5 days/week, for up to 2 years. The crystalline silica was described as somewhat coarser than the amorphous form; approximately 50% of the crystalline silica and 70% of the amorphous material were less than 4 μm in diameter. In the experiment with cristobalite, pulmonary fibrosis was observed first in guinea pigs after 15 mo; this condition became more severe after 21 mo. In the experiment with diatomaceous earth, fibrosis was first noted after 24 mo and was never as severe as it was with cristobalite.

Rosenbruch et al. (1990) compared the fibrogenic effects of quartz (DQ-12) and amorphous fused silica (quartz glass VP 203 to 006) by exposing two groups of 35 male Wistar rats to 10 mg/m^3 of each chemical, 7 h/day, 5 days/week for 12 mo. Thirty rats served as controls. The particle size of 99% of the quartz dust was <4 μm, with 50% of particles having a particle size of 0.40 μm. A similar particle size distribution was reported for amorphous silica. Some animals were sacrificed serially (5 rats/group after 4 and 8 mo of exposure, 15 rats/group and 10 controls after 12 mo of exposure); the remaining rats were observed for another 12 mo postexposure.

Exposure to silica did not affect body-weight gain. The relative lung weights of rats exposed to amorphous silica were comparable to those of controls, but lung weights of

quartz-exposed rats were increased markedly, particularly at 12 and 24 mo (12 mo exposure and 12 mo postexposure). Also seen at the end of the same time points were increased mediastinal lymph node weights in both quartz- and amorphous silica-exposed rats. Compared with controls, quartz-exposed rats had increased levels of serum lysozyme (an indicator of macrophage alterations) commencing at Month 8, and liver enzyme glutamate oxaloacetic transaminase activity increased at 12 and 24 mo (12 mo postexposure); microscopic examination of the liver showed no morphological changes. Serum chemistry was not altered in rats exposed to amorphous silica. Histologic examination of lungs showed qualitatively similar changes for both exposure groups; however, quartz-exposed rats exhibited more severe alterations. At 4 mo, there were slight cellular alterations (macrophage infiltration and appearance of neutrophilic granulocytes); at 8 and 12 mo, a few collagenous fibers and diffuse structural changes, including interstitial fibrosis, were noted. At the end of the 12-mo observation period, pronounced fibrosis and granulomatous inflammatory reactions occurred in quartz-exposed rats. Histomorphologic changes, characterized as diffuse foci containing macrophages, epithelial cells, fibroblasts, and collagen fibers, also were observed in the mediastinal lymph nodes of both exposure groups. Again, these effects were more severe in the group exposed to quartz. No morphological lung changes occurred in controls.

Warheit et al. (1995) evaluated the relative pulmonary toxicity of short-term inhalation of quartz (Min-U-Sil™), cristobalite, amorphous silica (Zeofree™ 80), and Ludox™ colloidal silica particles. CD rats were exposed for 3 days to aerosol concentrations ranging from 10 to 100 mg/m^3 of quartz, cristobalite, or amorphous (Zeofree™ 80) silica particles (MMADs not given). Also, CD rats were exposed for 2 or 4 weeks at concentrations of 10, 50, or 150 mg/m^3 to Ludox™ colloidal silica particles (MMADs not given). The brief exposures to quartz and cristobalite produced a pulmonary inflammatory response (PMN recruitment and consistently elevated biomarkers of cytotoxicity in BAL fluids) that persisted throughout a 3-mo postexposure period. Progressive histopathologic lesions have been observed within 1 mo after a 3-day exposure (Warheit et al., 1991b). In contrast, 3-day exposure to amorphous silica particles produced a transient pulmonary inflammatory response (present 24-h postexposure, but not detectable 8 days postexposure), and 2- or 4-week exposures to Ludox™ produced pulmonary inflammation (increased numbers of lavaged PMNs) at 50 and 150 mg/m^3 but not at 10 mg/m^3. The response was reduced in these two groups by approximately one order of magnitude after the

3-mo postexposure period. These results demonstrate that, although amorphous silica does cause a transient inflammatory response, even brief exposures to crystalline silica are much more potent in producing persistent pulmonary toxicity in comparison to amorphous or colloidal forms of silica.

7. ESTIMATION OF POTENTIAL HEALTH RISK FROM AMBIENT SILICA EXPOSURES, USING DATA FROM OCCUPATIONAL STUDIES

A broad range of effect levels, primarily LOAELs, from both human and animal studies are presented in Chapters 5 and 6. Human studies are among silica-exposed workers, and the health effects are for silicosis, a well-recognized respiratory disease in humans. In keeping with EPA risk assessment methods (U.S. Environmental Protection Agency, 1994a), such occupational dose-response data are preferred. The animal findings are considered useful qualitatively, but, because laboratory animals generally are exposed to doses one or more orders of magnitude higher than that which has been observed occupationally and several orders of magnitude higher than that which is expected in the ambient environment, they are not as useful quantitatively as are the human occupational studies. Human data provide a more direct answer to the question, how much risk does silica play in a PM_{10}-pulmonary disease relationship?

Table 7-1 summarizes the key epidemiologic studies that lend themselves to a quantitative analysis. Because of the size of the cohorts, the use of longitudinal retrospective study designs, and the use of a similar, high quality statistical approach to the representation of silicosis risk from silica exposure, the studies of white South African gold miners, Canadian hardrock miners, and South Dakota gold miners are considered the most reliable basis for risk assessments. The exposure-response curves reported in these studies (provided in Chapter 5 as Figures 5-1 through 5-3) are overlayed in Figure 7-1 (Canadian curve depicts average of risks predicted by readers 2 and 3 of Muir et al., 1989b).

To approximate the silicosis risk associated with ambient exposures from these curves, ambient levels must first be adjusted to approximate 8-h occupational exposure equivalents. In Chapter 3, average and high ambient concentrations of crystalline silica in the United States were estimated to be 3 and 8 $\mu g/m^3$, respectively. Consistent with EPA dose-response assessment methods (U.S. Environmental Protection Agency, 1994a), continuous (24-h) exposure to 3 and 8 $\mu g/m^3$ are assumed to pose the same health risk as 8-h occupational exposures to 8.4

TABLE 7-1. SUMMARY OF OCCUPATIONAL STUDIES OF SILICOSIS RISK

Reference	Study Type[a]	Study Population	Health Effect	% Silica (Quartz)
Hnizdo and Sluis-Cremer (1993)	LRC	2,235 South African miners; started after 1938 and worked ≥10 years; followed to 1991.	313 cases of silicosis (ILO Category ≥ 1/1)	30
Muir et al. (1989a,b), Muir (1991), Verma et al. (1989)	LRC	2,109 Canadian miners; started 1940 to 1959; followed to 1982 or end of exposure.	32 cases of silicosis (ILO Category ≥ 1/1)	6.0 to 8.4
Ng and Chan (1994)	XRC	338 Hong Kong granite workers; 132 past workers (1967 to 1985) and 206 current workers (1985); only most recent X rays examined.	36 radiographical abnormalities, rounded opacities (ILO Category ≥ 1/1)	27
Rice et al. (1986)	CC	U.S. (North Carolina) dusty trades workers diagnosed with silicosis, 1935 to 1980.	216 cases of silicosis; 672 controls	1 to 50
Steenland and Brown (1995b)	LRC	3,330 South Dakota gold miners who worked at least 1 year underground between 1940 and 1965; followed to 1990.	170 cases of silicosis (ILO Category ≥ 1/1)	13

[a] CC = Case control, L = Longitudinal, RC = Retrospective cohort, X = Cross-sectional, Q = Quartz.

and 22.4 $\mu g/m^3$, respectively (continuous exposures = TWA occupational exposures × [5 days/7 days] × [10 m^3 air breathed at work/20 m^3 total air breathed in a day]). A 70-year exposure to these occupational equivalents would result in cumulative silica exposures of 0.6 and 1.6 mg silica/m^3 × years, respectively (cumulative exposure = occupational equivalent exposure × 70 years). The South African, Canadian, and South Dakota studies predict a cumulative silicosis risk of very close to 0% for a cumulative silica exposure of 0.6 mg/m^3 × years. However, the estimates of cumulative risk diverge at higher cumulative exposure levels.

At 1.6 mg/m^3 × years, the South Dakota study predicts an 8% cumulative silicosis risk; the South African study predicts 2%, and the Canadian study predicts 0.4%. At higher exposure levels, the South Dakota and South African studies converge, but the Canadian study does not. In addition, the South Dakota and South African results appear to be more consistent with the results of other studies in the United States (Theriault et al., 1974c) and Hong Kong (Ng and Chan, 1994). The Theriault et al. studies are disputed elsewhere (Graham et al., 1991).

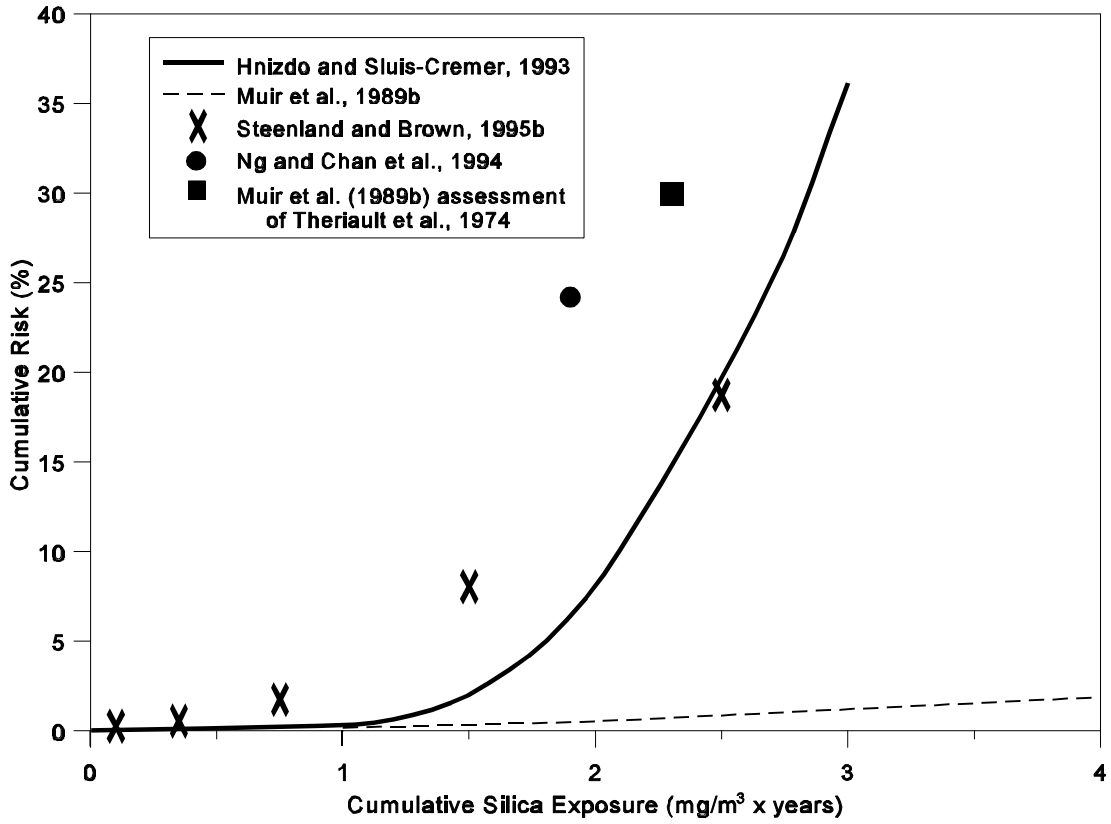

Figure 7-1. Cumulative silica risk curves estimated for South African gold miners (—) (Hnizdo and Sluis-Cremer, 1993) and Canadian hardrock miners (– –)(Muir et al., 1989b); cumulative silica risk points estimated for South Dakota gold miners (✗) (Steenland and Brown, 1995b), Hong Kong granite workers (●) (Ng and Chan, 1994), and Vermont granite miners (■) (Theriault et al., 1974c; Muir et al., 1989b).

However, Muir et al. (1989b) themselves state that the data from studies of Vermont granite miners (Theriault et al., 1974c) suggest that "...the true probability of developing category 1 [on the 1972 ILO scale] pneumoconiosis after 46 years of exposure to 0.05 mg/m^3 of respirable silica [a 2.3 mg/m^3 × years cumulative exposure] might be about 30%." Ng and Chan (1994) reported that 24% of the X rays of Hong Kong granite workers who received an average cumulative silica exposure of 1.9 mg/m^3 × years contained rounded opacities indicative of silicosis. As can be seen from Figure 7-1, these estimates of risk are well above the <1% cumulative risk of silicosis predicted by Muir et al. (1989b) for a cumulative exposure of 2 mg/m^3 × years, but are consistent with the 10 to 20% risk and the shape of the exposure-response curves reported by Hnizdo and

Sluis-Cremer (1993) and Steenland and Brown (1995b). Also, a recently completed Italian study of male workers employed in the ceramics industry (Cavariani et al., 1995) reports a 48% cumulative risk of silicosis (95% CI, 41.5 to 54.9) after 30 years of employment (past exposure levels not given, but estimated to be 3 to 5 times higher then the current 0.1-mg/m^3 standard). The authors reported that their risk estimates were higher than those predicted by Muir et al. (1989b), but "were consistent with the findings among South African gold miners." Thus, the South Dakota and South African studies are preferred over the Canadian studies.

It could be argued that the use of death certificate information in the South Dakota study represents a more sensitive diagnosis method than X rays because of the low sensitivity of X rays in the diagnosis of silicosis (Hnizdo et al., 1993). However, the fact that the South African study was continuous and longitudinal and involved multiple X-ray examinations per miner helps to compensate for this lack of sensitivity and reduces the potential for false negatives. Death certificates were available for only about half of the South Dakota cohort that died before the end of the study; the remaining cohort (i.e., miners living at the end of the study) did not receive X-ray examinations as often as did the South African miners (100% of the South African miners versus 25% of the South Dakota miners were x-rayed). Further, autopsy data available in the South African study allow for a more accurate interpretation of radiographic results. It is for these reasons that, although the data from the South Dakota study are certainly supportive, the data from the South African gold mines study were used in the following benchmark dose (BMD) analysis.

A BMD dose analysis is defined as the use of a specific mathematical model to determine a concentration (applied dose) and its lower confidence bound (e.g., 95% confidence limit) that is associated with a predefined effect level (U.S. Environmental Protection Agency, 1994a). The purposes of the BMD analysis performed on the Hnizdo and Sluis-Cremer (1993) data set were twofold. First, the BMDs associated with 1, 5, and 10% risk of silicosis were derived, and, then, the upperbound risk levels associated with various exposure levels were calculated. The model used and the methods for deriving the BMDs and upperbound risk levels are described in Appendix B, "Benchmark Dose Analysis of Risk of Silicosis Using Data from South African Gold Miners." The results are presented in Table 7-2 and discussed below.

TABLE 7-2. OCCUPATIONAL RISK ESTIMATES FROM APPLICATION OF LOG-LOGISTIC MODEL TO DATA OF HNIZDO AND SLUIS-CREMER (1993)[a,b]

	CSE for Risk of:			Risk for CSE of:		
	1%	5%	10%	0.6	1.0	1.6
Best-fit estimates	1.39	1.97	2.30	0.019%	0.21%	1.9%
Lower bounds on CSEs	1.31	1.90	2.24	-	-	-
Upper bounds on risks	-	-	-	0.032%	0.30%	2.4%

[a]See Appendix B for a discussion of methods used for estimating these risk levels and confidence bounds.
[b]CSE = Cumulative silica exposure.
Notes: CSEs are measured in milligrams per cubic meters-years. Bounds are 95% lower bounds or 95% upper bounds, as appropriate.

The log-logistic cumulative risk model proposed by Hnizdo and Sluis-Cremer (1993) served as the foundation for the benchmark analysis. Per the authors report, silica was assumed to constitute 30% of the dust to which miners were exposed. To determine lower bound confidence limits on the cumulative silica exposures associated with 1, 5, and 10% risk of silicosis, a simulation procedure that mimics the progression of each cohort member through individual exposure history (see Appendix B) was employed. The simulation approach employed suggested that the BMD (lower bound on cumulative silica exposures [CSEs]) based on 1, 5, and 10% risk of silicosis was 1.31, 1.90, and 2.24 mg/m^3 years, respectively. Using the method discussed earlier in this chapter, these convert to continuous, lifetime (70-year) ambient exposures of approximately 6.7, 9.7, and 11.4 µg crystalline silica/m^3, respectively. The model also was used to calculate the 95% upper bound confidence limit on the risk associated with CSEs of 0.6, 1.0, and 1.6 $mg/m^3 \times$ years. The 1-mg/m^3 CSE corresponds to a maximum level of ambient crystalline silica exposure assuming continuous lifetime exposure to the EPA's annual PM_{10} NAAQS of 50 $\mu g/m^3$ and a 10% silica fraction (50 $\mu g/m^3 \times 10\% =$ 5 $\mu g/m^3 =$ 1 mg/m^3 year $\times$ 5/7 $\times$ 10/20 $\div$ 70 years). As discussed earlier, the 0.6 and 1.6 $g/m^3 \times$ year CSE estimated maximum CSE equivalents, assuming continuous exposure to average (3 $\mu g/m^3$) and high (8 $\mu g/m^3$) annual average quartz concentrations documented in the United States. The risks estimated for these three CSE equivalents were approximately 0.03, 0.30, and 2.40%, respectively.

These approximations must now be considered in light of other important epidemiological evidence. Rice and Stayner (1995) have suggested that the differences in the South African and Canadian studies at higher cumulative exposures are likely the combined result of several factors, including differences in the definition of radiographic silicosis used in the two studies, possible errors in exposure estimates, possible underestimation of the quartz content of the dust in the Canadian study, inhalation of aluminum dust as a protective measure by Canadian miners, reader variability, and the use of cumulative exposures to estimate risk. These and other issues associated with relating occupational studies to ambient silica exposure scenarios (e.g., the importance of tracking worker health beyond employment; the reliability of radiographs for diagnosing silicosis; the importance of surface properties, particle size distribution, and percentage of silica in the respirable dust fraction) are discussed in Chapter 8.

8. SUMMARY AND CONCLUSIONS

The primary purpose of this document is to summarize the noncancer health effects from inhaled amorphous and crystalline silica, focusing on data that characterize a dose-response relationship. This document also presents the limited information on ambient silica sources and air quality to provide an exposure perspective. Further evaluations would be required for a complete quantitative risk assessment involving the combination of quantitative-exposure and dose-response assessments.

Amorphous silicas have the same basic elements (silicon and oxygen) as crystalline silica, and both are solids at room temperature, but their physical forms and internal structures are very different. As was discussed in Chapter 1, in a crystalline substance (such as quartz), the atoms are arranged in a repeating pattern of silica tetrahedra. The distinguishing feature of a crystalline substance is that one can take any portion of it and see the whole. The atoms in amorphous silicas are arranged randomly. The most outstanding characteristics of amorphous silicas, particularly synthetic amorphous silicas, are their small particle size, high specific surface area, and high solubility (relative to crystalline silica). Although limited data on ambient air concentrations of amorphous silica exist, the toxicologic characteristics of amorphous silicas are characterized fairly well as being less toxic than crystalline forms in experimental animals. However, added research is needed on this topic (Rabovsky, 1995). The smaller particle size and higher specific surface area of these substances generally result in increased cytotoxicity and more severe acute effects than crystalline silica (Pandurangi et al., 1990). The higher cytotoxicity of silica particles of respirable size has been related to the chemical interaction of functional groups on the surface of such particles with the lipoproteins contained in cell membranes (Pandurangi et al., 1990). Although cytotoxicity varies greatly with crystalline structure, particle size, surface composition, and molecular surface configuration, only crystalline forms can induce silicosis (Reuzel et al., 1991; Pandurangi et al., 1990). Although amorphous silicas have been shown to produce such effects as granulomatous lesions, influx of PMNs, and swollen and spotted lymph nodes, they have been reported in animal studies to have no or little fibrogenicity (Reuzel et al., 1991; Groth et al., 1981). Further, observed effects from exposure to amorphous silicas are

reversible with cessation of exposure. This largely is due to the higher solubility and increased rate of clearance from the lungs of amorphous silicas.

Of the three forms of inhalable amorphous silica, only silica F has been studied in both animals and humans. Occupational exposure to high, but unmeasured concentrations of the fumes of amorphous silica is associated with recurrent fever reminiscent of metal fume fever (Taylor and Davies, 1977; Princi et al., 1962). X-ray changes similar to those observed in silicosis cases also occur, but these changes do not progress, and, in many cases, they regress or resolve spontaneously. Silica P is even less toxic and may even mitigate the toxic action of quartz (American Conference of Governmental Industrial Hygienists, 1991). The American Conference of Governmental Industrial Hygienists' threshold limit values (TLVs) for silica F and silica P are 2 and 10 mg/m^3, respectively.

Citing the absence of any studies that examine the potential health effects of inhaled fused silica in either laboratory animals or humans, the American Conference of Governmental Industrial Hygienists (1991) determined that fused silica could be expected to be "nearly, if not quite, as fibrogenic as that of crystalline quartz" and, thus, assigned fused silica the same TLV as crystalline quartz, 0.1 mg/m^3. This is based on data from intratracheal exposure studies in rats that indicate the potential for fibrosis from exposure to fused silica (King et al., 1953; Englebrecht et al., 1958; Swensson, 1967). The recent comparative inhalation study by Rosenbruch et al. (1990) (Chapter 6, Section 6.4) clearly indicates, however, that fused silica is considerably less toxic than crystalline silica.

The animal data discussed in Chapter 6 and summarized in Table 6-1 are qualitatively useful. These studies identify potential immunologic effects, principally at higher exposures (Burns et al., 1980; Scheuchenzuber et al., 1985), yet support the choice of silicosis as the critical effect given its observation at lower exposure levels. They also emphasize the progressive nature of the fibrotic lesions associated with silicosis (Muhle et al., 1989; Kutzman, 1984a,b), and the difficulties associated with X-ray diagnosis (Kutzman, 1984a,b). However, in most cases, only one dose level was examined, and no NOAELs were identified. A fully developed and verified, physiologically based model of silica deposition and clearance from the lungs following inhalation would be useful towards converting the effect levels observed in laboratory animal studies to human equivalent concentrations and verifying the estimates provided in Table 6-1. Several researchers have attempted to model various aspects of the kinetics of inhaled quartz dust

(Vincent and Donaldson, 1990; Vincent et al., 1987; Smith, 1985; Oghiso et al., 1986; Jones et al., 1988; Katsnelson et al., 1992; Stöber, 1993). Many of these models are in preliminary stages of development. In general, they are not physiologically based and do not account adequately for the reported altered clearance caused by the inherent toxicity of crystalline silica to alveolar macrophages (Jones et al., 1988), particularly at exposure levels not associated with particle overload. They suffer from the lack of chronic studies exposing laboratory animals to more than one exposure level and the lack of a good animal model for the silicotic effects observed in humans, which have been reported to be histopathologically different from those observed in rodents (Muhle et al., 1989). Thus, the available models are currently not practical nor useful towards improving estimates of human equivalent concentrations extrapolated from laboratory animal studies. Considering all of these limitations, laboratory animal studies are not an appropriate basis for EPA's silica dose-response assessment.

A database, including adequate ambient and occupational human studies, is preferred for a dose-response assessment. However, unlike the PM_{10} air pollution and human health literature, ambient silica exposures and human health research must be characterized as tentative and suggestive. By contrast, there is a body of well-controlled occupational silica studies available for analysis. Important issues to reconcile include the large divergence of risk estimates within the occupational setting (particularly at high cumulative exposures) and methods to extrapolate risk in an occupational setting to risk from ambient exposure. The remainder of this chapter will address these issues, beginning with the former issue.

For the most part, studies of Canadian miners and North Carolina dusty trades workers were based on X-ray data obtained during employment. This could have led to a significant under-diagnosis of silicosis by these investigators. The importance of extensive follow-up beyond employment was illustrated by Steenland and Brown (1995b), Hnizdo et al. (1993), and Hnizdo and Sluis-Cremer (1993). The system in South Africa (i.e., monetary compensation to workers and their families based on the degree of silicosis contracted in the mines) results in a large percentage of white South African gold miners continuing to receive radiologic examinations beyond employment (the study population average year of last dust exposure was 1972, and the average year of last X ray was 1978). In addition, 85% of the miners who died had an autopsy to determine the degree of silicosis (Hnizdo et al., 1993). Hnizdo and Sluis-Cremer (1993) observed that of 313 miners determined to be silicotic through X-ray diagnosis, 178 (57%)

were first diagnosed (ILO Category ≥ 1/1) an average of 7.4 years after leaving the mines at an average age of 59. In contrast, all of the cases in the Muir et al. (1989a,b) study were diagnosed during employment at an average age of 52 years. Considering that less than half (43%) of the cases in the South African study were identified during employment, the incidence of silicosis is likely to have been significantly underdiagnosed in the Muir et al. (1989a,b) study.

Further emphasizing the need for frequent and improved follow-ups, Hnizdo et al. (1993) found that, despite an average time between the date of last X ray and death of just 2.7 years, the best of three X-ray readers did not diagnose silicosis in 61% of 326 cases categorized at autopsy as slight to marked silicosis. A similar lack of concurrence between X-ray and histopathologic indicators of silicosis has been noted during early stages of silicosis in experimental laboratory animal studies (Kutzman, 1984a,b). Hnizdo et al. (1993) suggested that the lack of concurrence they observed may have been due to problems inherent to the reading of even the best radiographs, as well as to problems with reader variability and film quality. Similar concern was expressed over the quality and age of X rays examined by investigators of both Canadian (Muir et al., 1989a) and North Carolina (Amandus et al., 1992) workers. These observations also suggest a possible underdiagnosis of silicosis in these studies.

Muir et al. (1989a) also indicated that many Canadian hardrock miners in their study had inhaled finely divided aluminum dust prior to underground work as a prophylactic measure. They expressed concern that "...cessation of aluminum therapy could have led to unmasking of silicotic lesions after the miners left the industry." This concern appears to be justified in that a recent study by Dufresne et al. (1994) reported a clear reduction in the pulmonary retention of quartz in sheep that inhaled aluminum lactate at 1-mo intervals following quartz exposure. Other dusts may also inhibit the silicotic effect of quartz. Muir (1994) has suggested that the low risk identified by their previous research study may have been due to a low level of quartz in the respirable dust.

Thus, factors that may have led to diagnostic differences in the South Dakota, South African, Canadian, and North Carolina studies include the extent of follow-up beyond employment; the quality of chest X rays; the qualification of radiologists to read the films; and mining procedures and prophylactic measures that may have prevented, masked, or obscured silicotic lesions.

Although diagnostic difficulties may account for some differences, they are not likely to account fully for the marked differences in silicosis risk estimates. Hnizdo and Sluis-Cremer

(1993) raised the possibility that the average dust concentrations used in their study may have underestimated the actual exposures. Steenland and Brown (1995b) had to estimate silica exposures prior to 1937 without actual dust measurements. Muir et al. (1989b) indicated that the dust concentrations they used may have overestimated the average exposures of individual miners, resulting in an underestimation of risk. No basis is provided for quantitatively estimating the impact of these potential errors, but, taken together, they would tend to bring the risk estimates of the studies closer together.

Other factors that can reduce or enhance the risk of health effects should be considered on a case by case basis. Particle size and surface properties are known to be important factors in the toxicity of silica (Davis, 1986; Shi et al., 1989; Silicosis and Silicate Disease Committee, 1988). Silica particles resulting from mining tasks are small in size (Verma et al., 1994). In the study of Canadian hardrock mines, 5 to 16% of the silica collected during five different mining operations were smaller than 2 μm aerodynamic diameter. If, as is indicated by an earlier report by Davis et al. (1984), ambient quartz is almost completely absent from the fine (≤2.5 μm aerodynamic diameter) fraction of particulate matter, risk to the general public could be less than is predicted from occupational studies, which were based on worker exposure to particles ≤5 μm aerodynamic diameter, a substantial fraction of which was < 2.5 μm aerodynamic diameter (Verma et al., 1994). Figure 8-1 shows the overlap between the ranges of fractions of particle sizes that deposit in pulmonary tissue (nose or mouth breathers) and the ranges of fractions of particle sizes measured in the mining environment air. It clearly shows the important relation between particle size and pulmonary deposition and that a vast majority of airborne silica in the mining environment is of the size that is likely to be deposited. Although completely comparable data are not available for the ambient environment, Table 3-7, taken from Davis et al. (1984), indicates that fine (≤2.5-μm) silica in the ambient environment generally represents less than 10% of total dichotomous mass (particles ≤ 15 μm) and likely would represent a much smaller percentage of TSP.

Further, the general public may not be exposed to as much freshly ground or fractured quartz particles as are miners. Freshly ground quartz has been found to be much more cytotoxic than aged quartz because grinding or fracturing quartz particles is thought to break the silicon-oxygen bonds, generating silicon and silicon oxide radicals on the surface of the particles. These surface radicals decay as fractured silica dust is aged (Vallyathan et al., 1988, 1995;

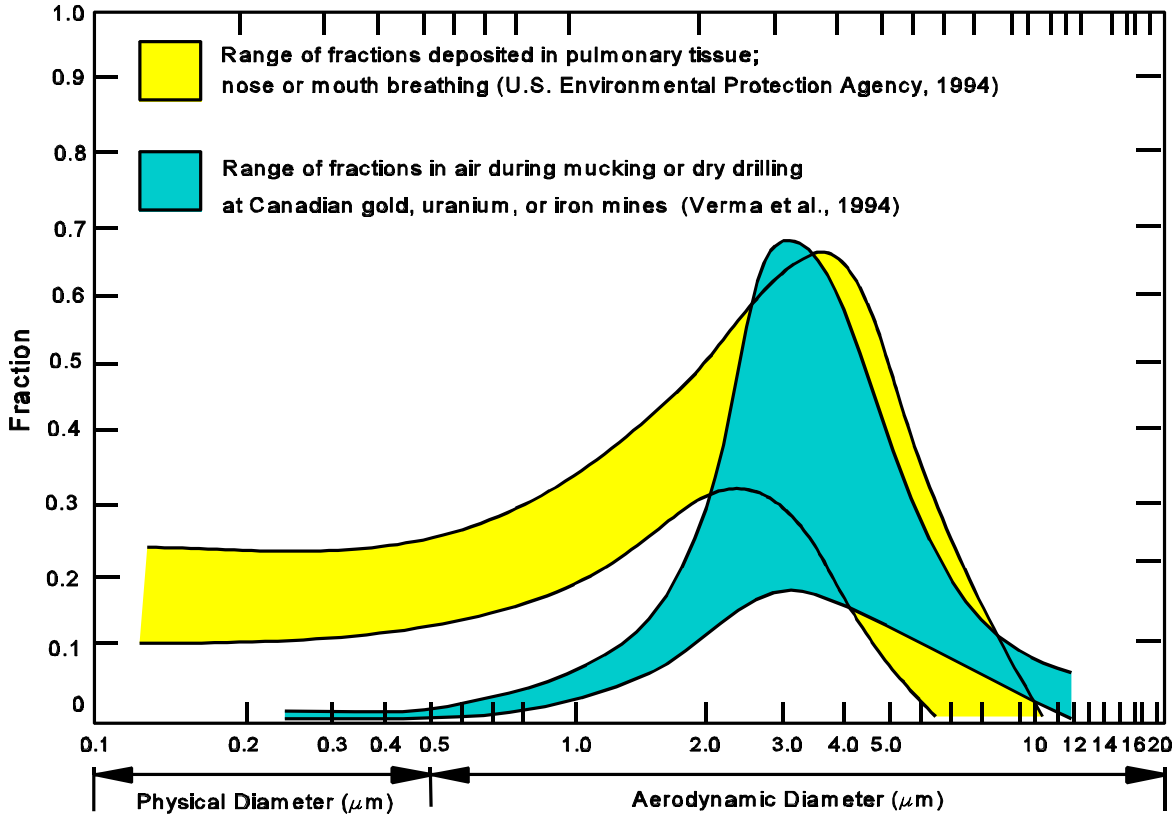

Figure 8-1. Overlay of pulmonary particle deposition curves and particle size distributions reported for silica (quartz) in various mining operations.

Vallyathan,1994; Shoemaker et al., 1995). This may be one reason that extremely high exposures to desert dust have resulted in more benign conditions referred to as "simple siliceous pneumoconiosis" (Bar-Ziv and Goldberg, 1974), "desert lung syndrome" (Nouh, 1989) and stage I silicosis (Xu et al., 1993).

It is possible that differences in the physical properties and the fraction of quartz present in Canadian hardrock mines, North Carolina dusty trades, and South African gold mines could account partially for the differences in toxic potency observed. Because the exposure assessments were performed retrospectively, limited data are available regarding the particle characteristics of the quartz involved. Data do indicate, however, that the silica content in the rock being mined may have differed. The rock mined in South African gold mines contains 60 to 90% crystalline silica in the form of quartz (Hnizdo et al., 1993). Muir (1994) has suggested that a higher fraction

of silica in the respirable dust of the South African mines (reported to be 30% by Hnizdo and Sluis-Cremer, 1993) versus the Canadian mines (reported to be 6 to 8.4% by Vermal et al., 1989, and Muir, 1994) contributed to the disparity between the two studies.

Other exposure factors that should be considered include the duration and period of exposure during an individual's life span and the dose-rate pattern. Duration and period of exposure are important because the risks of developing radiological signs of silicosis have been shown to increase with age, even after the termination of exposure (Hnizdo and Sluis-Cremer, 1993). It is also possible that the use of cumulative exposure units may ignore differences in risk resulting from different dose-rate patterns. Checkoway and Rice (1992), in a reanalysis of the North Carolina dusty trades cohort, showed that peak exposures may be a better predictor of silicosis risk than cumulative exposures. From personal monitor data, Pellizzari et al. (1992) showed that individuals who engaged in certain household activities (vacuuming, dusting, cooking, etc.) had higher overall PM_{10} and silica exposures, suggesting that, although indoor silica levels, as measured by stationary monitors, may be lower than outdoor levels, peak exposures from indoor activities contribute significantly to an individual's overall cumulative exposure.

Although there are several issues and inconsistencies that remain to be resolved, the current studies are consistent with respect to several factors relevant to the potential for health effects from ambient exposures to crystalline silica. All of the studies point out difficulties with diagnosing silicosis from X-ray information. The Hnizdo et al. (1993) study further indicates that the diagnostic sensitivity of radiological tests could be improved by using ILO category 0/1 as a cutoff point for individuals who have been exposed to average-to-high concentrations of respirable silica dust, and using categories 1/0 or 1/1 for individuals who have been exposed to low-to-average concentrations of respirable silica dust. The Canadian, South Dakota, and South African studies show that the risk of chronic silicosis increases exponentially with increasing cumulative dose of silica dust. It is clear that the onset of silicosis is age dependent, occurs predominantly after 50 years of age, and can continue to progress after exposures have ceased.

Gaps still exist in the database of information pertaining to the potential for health effects from ambient silica exposures, particularly with respect to populations other than adult male miners. However, some evidence is accumulating that suggests environmental pulmonary disease research may offer new insights into the question of ambient silicosis. Data from New Jersey

(Valiante and Rosenman et al., 1989) suggest that a better surveillance system for monitoring cases of silicosis is needed and that, currently, annual incidence is underestimated significantly. Further investigation is needed for some potentially sensitive subgroups, including infants and individuals with a respiratory infection or disease such as tuberculosis and pneumonia (Chapter 5, Section 5.2.4). Discrepancies in the epidemiologic reports appear troublesome. However, where the data disagree, greater weight should be given to the studies of South African miners because of the higher quality and completeness of follow-up compared to the other studies and the fact that the reported results are most consistent with the entire body of available literature. Consequently, a more in-depth, BMD analysis was performed on this set of data to determine the 95% confidence lower bounds on CSEs associated with 1, 5, and 10% risk and the 95% upperbound confidence limits on the risk estimated for CSEs of 0.6, 1, and 1.6 mg/m^3 years. These latter values represent continuous lifetime exposures to 3 $\mu g/m^3$ (estimated average crystalline silica level in U.S. metropolitan areas), 5 $\mu g/m^3$ (highest crystalline silica exposure assuming compliance with 50 $\mu g/m^3$ PM_{10} NAAQS and 10% crystalline silica fraction), and 8 $\mu g/m^3$ (estimated high crystalline silica level in U.S. metropolitan areas), respectively. Even with the conservative assumption that the ambient environment is not markedly different from the mining environment (e.g., with respect to duration of exposures, particle character, and size distribution) the estimated risk to healthy individuals continuously exposed for 70 years to 8 μg crystalline silica/m^3 is below 3%. We know, however, that the ambient environment is different in most cases from mining environments. These differences generally suggest that silica in the ambient environment is less toxic, primarily because of the larger particle sizes associated with ambient sources discussed in Chapter 3, the reduced likelihood of exposure to more potent "freshly fractured" silica, and less frequent peak exposures. The assumption of a full 70-year continuous exposure to high outdoor levels also is expected to result in a high estimate of risk under most circumstances. The fact that silicosis represented such a small percentage of interstitial lung diseases reported by Coultas et al. (1994), using clinical and autopsy records from a New Mexico mining county, may be further indication that the actual risk is lower. It is impossible to determine, however, the extent that silica may have contributed to other interstitial lung diseases identified in this report. In any case, a thorough analysis of the most extensive occupational studies available, each of which examined the medical histories of thousands of miners, suggests that the cumulative risk of silicosis among these South Dakotan, Canadian, and

South African miners from exposures at or below 1 mg crystalline silica/m^3 years is close to 0%. Using a high estimate of 10% for the crystalline silica fraction in PM_{10} from U.S. metropolitan areas, 1 mg crystalline silica/m^3 years is the highest CSE expected from continuous lifetime exposure at or below the annual PM_{10} NAAQS of 50 $\mu g/m^3$. Thus, current data suggest that, for healthy individuals not compromised by other respiratory ailments and for ambient environments expected to contain 10% or less crystalline silica fraction in PM_{10}, maintenance of the 50 $\mu g/m^3$ annual NAAQS for PM_{10} should be adequate to protect against silicotic effects from ambient crystalline silica exposures.

9. REFERENCES

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APPENDIX A
SILICA DUST LEVEL MEASUREMENT METHODS

Industrial hygienists for NIOSH have developed comprehensive methods for sampling crystalline silica levels in the workplace; however, sampling of ambient air for crystalline silica emissions is less well developed. The current methodologies for both occupational and environmental measurements of crystalline silica will be described in the following sections.

OCCUPATIONAL SAMPLING METHODS

Personal sampling commonly is performed using a variable-rate flow pump and a respirable dust cyclone. Samples are collected onto a cellulose diffuser membrane behind the filter. Sampling pumps are commonly worn on belts, and filters are placed in the breathing zone. Filters are connected to pumps by flexible plastic tubing and checked periodically during the day. For a person working on hazardous machinery, stationary sampling pumps may be placed away from the worker's activities, but at the same level as the worker's breathing zone. The amount of particulate matter is determined by weighing the filter paper after sampling and subtracting the before-use filter weight. Determination of silica percentage in dusts requires use of X-ray diffraction or infrared methods discussed later in this appendix. In general, multiple samples are taken in order to reflect differences in dust during different shifts and production times and using different industrial materials. When completed, mean values for dust mass concentrations in milligrams per cubic meter over 8-h shifts are reported (Lorberau and Abell, 1995). Although these methods have been used to estimate ambient crystalline silica levels, it may not be appropriate for this purpose because of the question of sensitivity in using occupational methods to estimate potential ambient exposures at lower concentration levels (Howard et al., 1991; McCormick, 1992).

AMBIENT SAMPLING METHODS

Ambient air sampling is often performed with dichotomous samplers. These samplers permit air samples to be divided into groups according to particle sizes. Common size selections include TSP and PM_{10}; fine and coarse PM_{10} (<2.5 μm and 2.5 to 10 μm, respectively); and respirable and nonrespirable PM_{10} (<5 μm and >5 μm, respectively). Sizes are adjusted by using different port diameters and filter membrane porosities (Reynolds et al., 1991).

Area monitoring pump flow rates can be set with rotameters built into the pump case. Polyvinyl chloride (PVC) filters are better than quartz filters for collection of dust to measure crystalline silica levels because they provide greater accuracy for X-ray assay methods (University of California at Davis, 1992). Sampling times and flow rates are variable and must be considered when total concentrations are calculated. After the samplers have collected suspended particulate materials, the filters are weighed to calculate the mass concentrations and analyzed using energy dispersive X-ray analysis (EDXA) to determine the concentration of various chemical elements (Moore, 1992).

Many factors, including air flows, particle sizes, and mathematics of sample placement, will affect particle measures. Furthermore, placement of pumps and samplers is critical to the interpretation of results but is rarely described. Studies by Gillette and co-workers (Gillette and Passi, 1988; Gillette and Hanson, 1989; Johnson et al., 1992) demonstrate that placement can alter greatly the quantities measured. External and physical factors of the monitoring devices themselves can add to measurement discrepancies. Placement and location of monitoring devices, their total number, and differences in technology can result in data discrepancies (U.S. Environmental Protection Agency, 1991b). Monitor placement and location greatly affect the measured emissions. Factors that are important are distance from the emissions source, elevation of the monitor, and location of the monitor in relation to wind-flow patterns. If monitoring devices are placed upwind from a source, they may underestimate mean emission concentrations; if downwind, they may overestimate mean emission concentrations. Monitor height above ground surface influences estimates of total particles and the relative distribution of particle sizes. Generally, the higher the monitor, the greater the relative fraction of PM_{10} within TSP due to the settling of larger particles, although the total quantity of particles may be reduced (Gillette and Hanson, 1989). Distance from an emission source will affect similarly the measured emissions because increasing distance gives larger and heavier particles more chance to settle (Johnson

et al., 1992; Gillette and Hanson, 1989). It has been observed that there is a nonuniform distribution of the components of particulate emissions with respect to size (Davis et al., 1984; Gillette, 1992b). For crystalline silica, the particle size distribution is such that particles >10 μm contain more crystalline silica than do particles <10 μm (Buckman and Brady, 1969; Davis et al., 1984; Gillette, 1992a).

SILICA ASSAY PROCEDURES

Silica can be measured within collected air samples, but there is not universal agreement regarding the best silica assay procedure. Many techniques are valid but are often cost prohibitive when it is necessary to perform repeated assays on a large number of samples. Some ambient sampling techniques of the early 1980s used samplers with quartz filters that were unable to discriminate between crystalline silica from the filter and that from the source being measured. More recent sampling techniques applied in the workplace use PVC or cellulose-based materials without quartz filters and permit testing without interaction. However, an economically valid analytic polycarbonate methodology for ambient silica dust sampling awaits development (McCormick, 1992). At present, there is controversy regarding silica assay methods, and it is likely that the existing methods will need verification as expertise is refined. California's "Hot Spots" silica monitoring requirements may result in improved measurement methods for both PM_{10} and crystalline silica.

Currently, the most common analytical technique is NIOSH Method 7500, which uses X-ray powder diffraction. The PVC filters are ashed in a muffle furnace (low-temperature RF plasma asher also is used), dispersed ultrasonically, and filtered onto silver membranes. Standards on silver membranes are then prepared from NIOSH reference quartz containing 20, 40, 100, 200, and 500 μg/filter. The silver membranes next are mounted on aluminum sample holders for X-ray analysis (National Institute for Occupational Safety and Health, 1994; Lorberau and Abell, 1995). Samples are analyzed with an X-ray defractometer using high-energy dispersive X rays. Both samples and standards are step-scanned at a scan rate of 0.01° per step and a counting rate of 10 s/step. Following correction on either side of the absorbance peaks, the area under the curve is integrated to obtain net counts for quartz and silver. Net counts are then adjusted for absorbance of X rays by the sample according to NIOSH Method 7500. Concentration of quartz is calculated

from the mass of quartz in each sample (from the standards calibration curve) and the volume of sampled air (National Institute for Occupational Safety and Health, 1994).

A technique that is sometimes used (but lacks accuracy) bases both PM_{10} and silica emissions estimates on soil analysis (Howard et al., 1991). Soil samples are collected and subsequently passed through mesh sieves of progressively smaller size. Material passing through a 400-point mesh is considered to be 10 μm or less. Particulates passing through the mesh may be subjected to EDXA but, more commonly, are examined microscopically for crystalline structure. On the basis of these measurements, silica and PM_{10} emissions are estimated assuming a linear relationship. These are techniques commonly applied in bulk mineralogic assays but are unacceptable to measure air pollutants, because there is not a direct linear relationship for emissions estimates among soil silica, PM_{10}, and air emissions (Howard et al., 1991).

APPENDIX B

BENCHMARK DOSE ANALYSIS OF RISK OF SILICOSIS, USING DATA FROM SOUTH AFRICAN GOLD MINERS

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INTRODUCTION

This report documents the methods for and results of applying BMD approaches to an epidemiological study of silicosis observed among South African gold miners who were exposed to silica (Hnizdo and Sluis-Cremer, 1993). The goal was to estimate the doses corresponding to possible benchmark levels of response and the lower bounds on those doses, which define the BMDs, using a model proposed by Hnizdo and Sluis-Cremer (1993). Their model relates cumulative dust or silica exposure to the risk of developing silicosis.

METHODS

The dose-response model proposed by Hnizdo and Sluis-Cremer (1993) is a log-logistic cumulative risk model that has the form

$$F(CD) = 1 - [1 + CD^{1/\sigma} * \exp\{-\mu/\sigma\}]^{-1},$$

where CD is cumulative dose (e.g., milligrams per cubic meters-years), F(x) is the cumulative probability of developing silicosis when exposure has entailed a cumulative dose of x, and the parameters σ and μ (also called the scale and the intercept, respectively) are estimated to best fit the data. The SAS® statistical analysis procedure LIFEREG was used by Hnizdo and Sluis-Cremer (1993) and in this analysis to implement the log-logistic model.

A preliminary analysis was conducted to determine whether the summary results presented by Hnizdo and Sluis-Cremer (1993) (see their Table IV) could be used to duplicate the results that they presented. Their results were for the application of the model above, but using cumulative total dust exposure rather than cumulative silica exposure as the CD term. Their results, presumably obtained using the individual data for each member of the cohort, were such that the intercept estimate was 2.439 (standard error estimate, 0.019), and the scale was 0.2199 (standard error estimate, 0.009). Our preliminary analysis results using the summary data in their Table IV gave estimates of 2.502 (standard error 0.018) and 0.2111 (standard error 0.009) for the intercept and scale, respectively. Because our results were extremely similar to those of Hnizdo and Sluis-Cremer (1993) our conclusion was that the summary data provided an excellent basis for pursuing the analysis of silicosis in relation to CSE.

Based on the suggestion of Hnizdo and Sluis-Cremer (1993), silica was assumed to constitute 30% of the dust to which the miners were exposed. Thus, the conversion from cumulative dust exposure to CSE was a simple multiplication of the former by 0.30.

The log-logistic model was fit to the calculated CSE and silicosis response data (Table B-1, adapted from Table IV of Hnizdo and Sluis-Cremer, 1993) using SAS procedure LIFEREG; CSE was used for CD in the model above. This original fit provided estimates of μ and σ, and, based on those estimates, of the CSEs associated with 1, 5, and 10% risk of developing silicosis, as well as the cumulative risk associated with CSEs of 0.6, 1.0, and 1.6 mg/m^3 years.

TABLE B-1. ORIGINAL CUMULATIVE SILICA EXPOSURE (CSE) AND SILICOSIS DOSE-RESPONSE DATA[a]

CSE Range	Number Affected[b]	Number Not Affected[b]	Total Number
(0.0, 0.6)	0 (1)	204 (2)	204
(0.6, 1.2)	9 (3)	465 (4)	474
(1.2, 1.8)	48 (5)	508 (6)	556
(1.8, 2.4)	85 (7)	384 (8)	469
(2.4, 3.0)	93 (9)	225 (10)	318
(3.0, 3.6)	53 (11)	89 (12)	142
(3.6, 4.2)	20 (13)	24 (14)	44
(4.2, 4.8)	5 (15)	6 (16)	11

[a]Based on Table IV of Hnizdo and Sluis-Cremer (1993), assuming 30% of dust was silica.
[b]In parentheses are the "group" numbers associated with each observation. See text for more discussion of groups. Those individuals who developed silicosis were considered to be affected; those who did not were considered unaffected.

To determine bounds on the CSEs associated with 1, 5, and 10% risk of silicosis, and bounds on the risk associated with CSEs of 0.6, 1.0, and 1.6 mg/m^3 years, a simulation procedure was employed. The procedure is described below.

Using the values of μ and σ from the original fit to the CSE data, simulated data sets were created as determined by the following algorithm:

a. Start with n1 through n16 all equal to 0.

b. Randomly generate 204 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n2 = n2 + 1$ otherwise.

c. Randomly generate 474 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n3 = n3 + 1$, if $F(0.6) < x \leq F(1.2)$
   $n4 = n4 + 1$ otherwise.

d. Randomly generate 556 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n3 = n3 + 1$, if $F(0.6) < x \leq F(1.2)$
   $n5 = n5 + 1$, if $F(1.2) < x \leq F(1.8)$
   $n6 = n6 + 1$ otherwise.

e. Randomly generate 469 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n3 = n3 + 1$, if $F(0.6) < x \leq F(1.2)$
   $n5 = n5 + 1$, if $F(1.2) < x \leq F(1.8)$
   $n7 = n7 + 1$, if $F(1.8) < x \leq F(2.4)$
   $n8 = n8 + 1$ otherwise.

f. Randomly generate 318 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n3 = n3 + 1$, if $F(0.6) < x \leq F(1.2)$
   $n5 = n5 + 1$, if $F(1.2) < x \leq F(1.8)$
   $n7 = n7 + 1$, if $F(1.8) < x \leq F(2.4)$
   $n9 = n9 + 1$, if $F(2.4) < x \leq F(3.0)$
   $n10 = n10 + 1$ otherwise.

g. Randomly generate 142 numbers (between 0 and 1). For each one, x,

   $n1 = n1 + 1$, if $x \leq F(0.6)$
   $n3 = n3 + 1$, if $F(0.6) < x \leq F(1.2)$
   $n5 = n5 + 1$, if $F(1.2) < x \leq F(1.8)$
   $n7 = n7 + 1$, if $F(1.8) < x \leq F(2.4)$

n9 = n9 + 1, if F(2.4) < x ≤ F(3.0)
n11 = n11 + 1, if F(3.0) < x ≤ F(3.6)
n12 = n12 + 1 otherwise.

h. Randomly generate 44 numbers (between 0 and 1). For each one, x,

n1 = n1 + 1, if x ≤ F(0.6)
n3 = n3 + 1, if F(0.6) < x ≤ F(1.2)
n5 = n5 + 1, if F(1.2) < x ≤ F(1.8)
n7 = n7 + 1, if F(1.8) < x ≤ F(2.4)
n9 = n9 + 1, if F(2.4) < x # F(3.0)
n11 = n11 + 1, if F(3.0) < x ≤ F(3.6)
n13 = n13 + 1, if F(3.6) < x ≤ F(4.2)
n14 = n14 + 1 otherwise.

i. Randomly generate 11 numbers (between 0 and 1). For each one, x,

n1 = n1 + 1, if x ≤ F(0.6)
n3 = n3 + 1, if F(0.6) < x ≤ F(1.2)
n5 = n5 + 1, if F(1.2) < x ≤ F(1.8)
n7 = n7 + 1, if F(1.8) < x ≤ F(2.4)
n9 = n9 + 1, if F(2.4) < x ≤ F(3.0)
n11 = n11 + 1, if F(3.0) < x ≤ F(3.6)
n13 = n13 + 1, if F(3.6) < x ≤ F(4.2)
n15 = n15 + 1, if F(4.2) < x ≤ F(4.8)
n16 = n16 + 1 otherwise.

For each of these steps (Steps b through i), the number of randomly generated numbers corresponded to the total number of cohort members with CSE in the ranges given in Table B-1. The n's correspond to the 16 groups of cohort members defined by their CSE and whether or not they developed silicosis. Group 1 includes those cohort members with CSE between 0 and 0.6 who developed silicosis, Group 2 includes those cohort members with CSE between 0 and 0.6 who did not develop silicosis, etc., as shown in Table B-1. Thus, n1 is the simulated number of individuals in Group 1, n2 is the simulated number of individuals in Group 2, etc.

When the simulated numbers were determined as described above, LIFEREG was used to fit the log-logistic model to the simulated data, and the CSE values corresponding to the designated risk levels and the risks associated with the desired CSEs were determined. This was repeated 1,000 times, resulting in distributions of CSEs corresponding to the 1, 5, and 10% risk levels as well as distributions for the risks associated with the CSEs of 0.6, 1.0, and 1.6 mg/m^3

years. The 5th percentiles of the distributions of CSEs corresponding to the 1, 5, and 10% risk levels were used as the estimators of the 95% lower bounds on the CSEs corresponding to those risk levels, and thus defined possible BMDs. The 95th percentiles of the distributions for the risks associated with the CSEs of 0.6, 1.0, and 1.6 mg/m^3 years were used to estimate the 95% upper bounds on risk for those CSEs.

RESULTS

For the log-logistic fit to the original CSE data (Table B-1), the maximum likelihood estimates (MLEs) of μ and σ were 1.298 and 0.2111, respectively. These estimates resulted in the CSEs and risks shown in Table B-2, designated the best-fit estimates. Figure B-1 displays the best fitting log-logistic curve.

TABLE B-2. RESULTS OF APPLYING A LOG-LOGISTIC MODEL TO DATA OF HNIZDO AND SLUIS-CREMER (1993) AND OF SIMULATIONS TO DETERMINE ESTIMATES OF CONFIDENCE BOUNDS

	CSE[a] for Risk of:			Risk for CSE[a] of:		
	1%	5%	10%	0.6	1.0	1.6
Best-fit estimates	1.39	1.97	2.30	0.019%	0.21%	1.9%
Lower bounds on CSEs[a]	1.31	1.90	2.24	-	-	-
Upper bounds on risks	-	-	-	0.032%	0.30%	2.4%

[a]CSE = Cumulative silica exposure.
Notes: CSEs are measured in milligrams per cubic meter-years. Bounds are 95% lower bounds or 95% upper bounds as appropriate.

When the simulation procedure was completed with 1,000 iterations, the medians of the CSEs associated with risks of 1, 5, and 10% were 1.386, 1.967, and 2.302, respectively, were extremely close to the original best-fit estimates of 1.389, 1.968, and 2.304, respectively. These results indicate the appropriateness of this procedure for developing BMD estimates. The 5th percentiles of the CSEs associated with the three risk levels are shown in Table B-2, and may be taken as the estimate of the BMDs associated with each of those risk levels. The relatively small

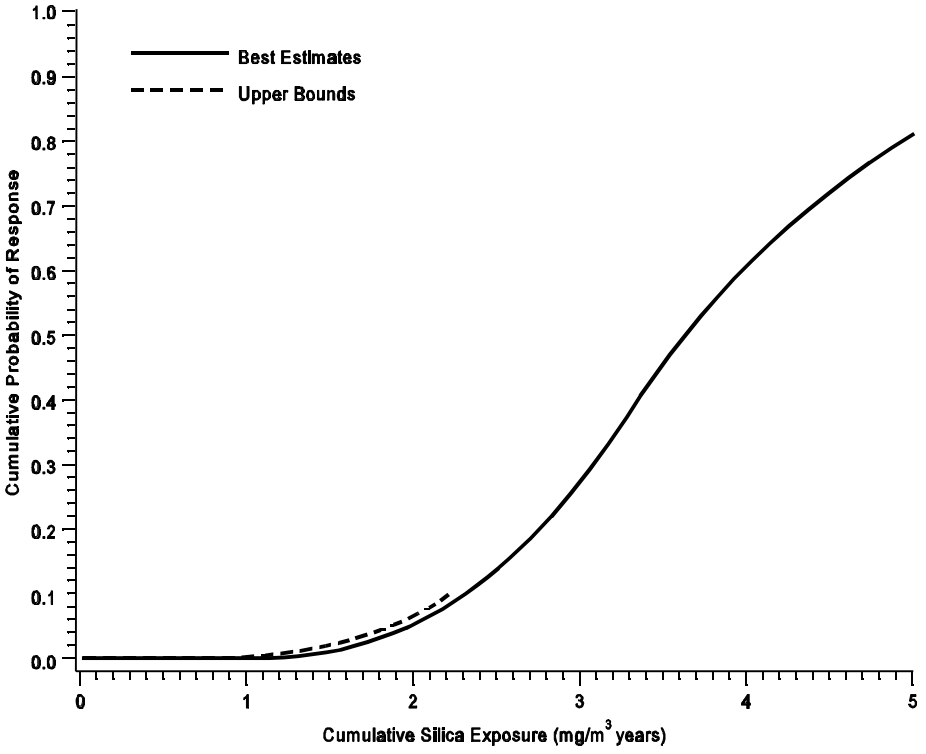

Figure B-1. Dose-response relationship for cumulative silica exposure and silicosis based on data from Hnizdo and Sluis-Cremer (1993).

differences between the best-fit estimates and the BMDs indicates the relatively small amount of uncertainty about the dose corresponding to those risks (assuming the correctness of the model). This is in part a function of the large number of observations (2,218 cohort members). When this simulation procedure was repeated, for the purposes of verifying the sensitivity of this approach to the number of observations, with a hypothetical cohort roughly 10 times smaller than the cohort identified by Hnizdo and Sluis-Cremer (1993), the 5th percentile of the distribution of CSEs corresponding to 10% risk (2.121) was indeed less than the BMD for that risk shown in Table B-2, and there was greater spread in the distribution of simulated CSEs corresponding to 10% risk. This sensitivity test procedure was not performed for the other risks or for the CSEs.

Also included in Table B-2 are the upper bounds on risks associated with CSEs of 0.6, 1.0, and 1.6. Similar to the results for the lower bounds on dose, the difference between the best-fit estimates and the upper bounds is relatively small.

Figure B-1 shows the approximate curve for the upper bounds on risk or lower bounds on dose. This curve was generated from the pairs of CSE/risk values listed in Table B-2, not including the best-fit estimates.

DISCUSSION

The simulation procedure used here is appropriate when there are no preprogrammed software packages that can be used to estimate analytically the lower bounds on doses corresponding to certain response levels or the upper bounds on risk corresponding to certain exposures. In this case, the procedure mimics the progression of each cohort member through that individual's exposure history. By sampling a number between 0 and 1 for each cohort member, it is possible to determine if the exposures up to each cut point defining the exposure categories (Table B-1) would have been sufficient to induce silicosis in that individual. This is analogous to a coin flip to determine whether an individual is considered "affected" or not "affected" (which would be appropriate, assuming a fair coin, if the chance of being affected were 50%). In this case the "flipping" is done by random number generations, and the results may have more than two possible outcomes. The outcome is the CSE category to which an individual is assigned, and the probability of being assigned to that category is equal to the risk of developing silicosis when exposures in that range have occurred (as estimated by the log-logistic model fit to the original observations). Of course, for some individuals, their exposure stopped before they reached some of the higher exposure categories, so they are assigned to the appropriate "not affected" groups (2, 4, 6,...) if the random numbers generated for them suggest assignment to an exposure category that they did not reach. As an example, for one of the 204 individuals who had CSE no more that 0.6, if the random number generated for him, x, indicated that he would have developed silicosis when his cumulative exposure was less than or equal to 0.6 (i.e., $x \leq F(0.6)$), then he was assigned to Group 1. However, if $x > F(0.6)$, then that result would suggest that he would have developed silicosis only for greater CSEs (if ever); since that individual did not have CSE greater than 0.6, he would be classified as not being affected by his exposure to CSE of up to 0.6 (i.e., he is assigned to Group 2).

The simulation approach employed here suggested that the BMDs based on 1, 5, and 10% risk of silicosis were CSEs of 1.31, 1.90, and 2.24 mg/m^3 year, respectively. This analysis did not consider models other than the log-logistic model. Hnizdo and Sluis-Cremer (1993) indicated that the log-logistic model fit their observations better than a Weibull model.